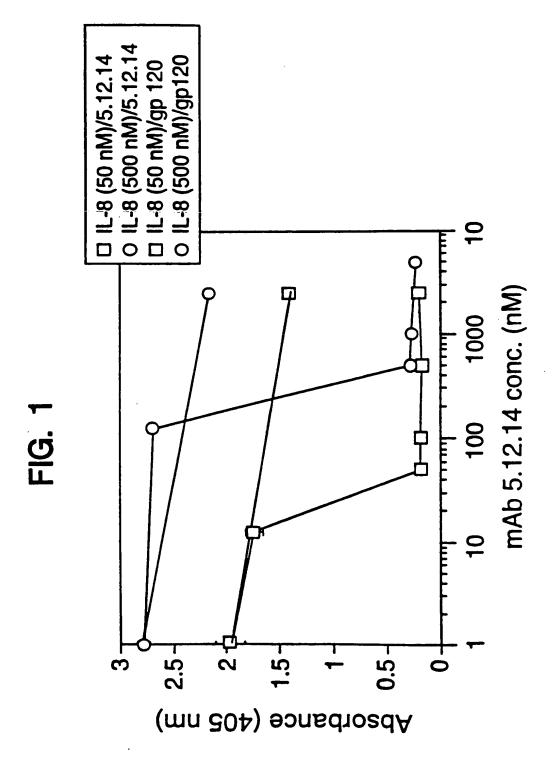
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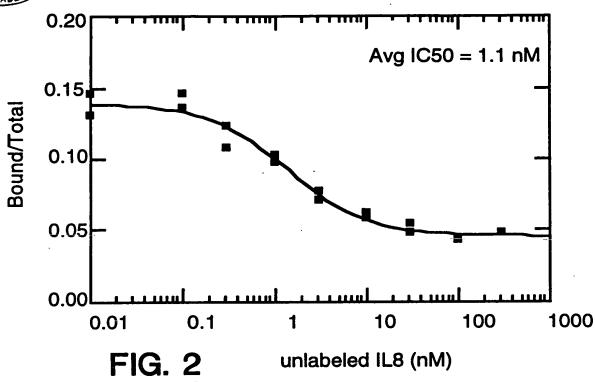


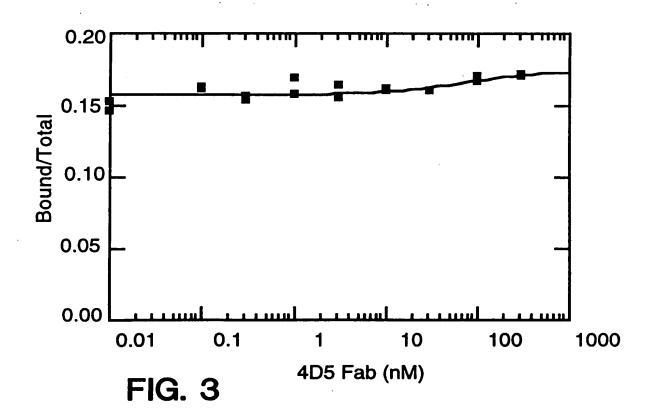


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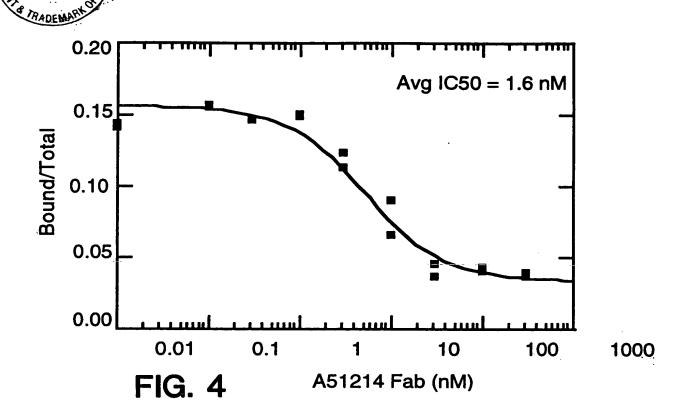


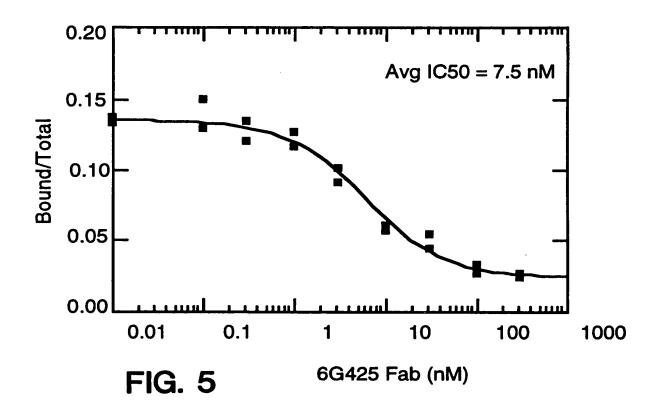




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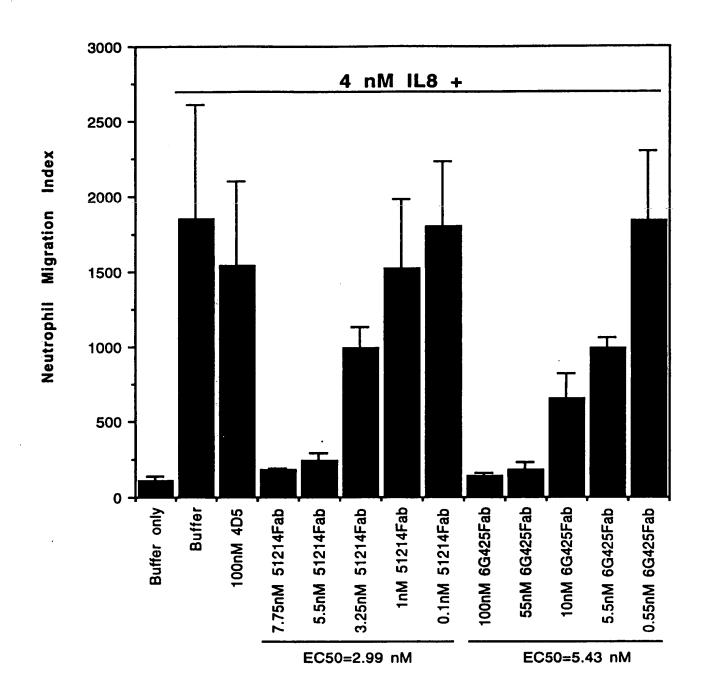


FIG. 6



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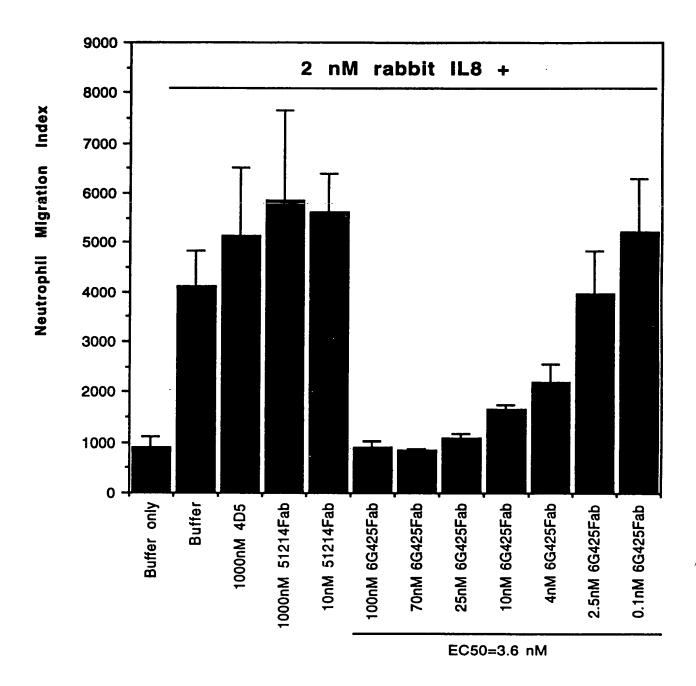
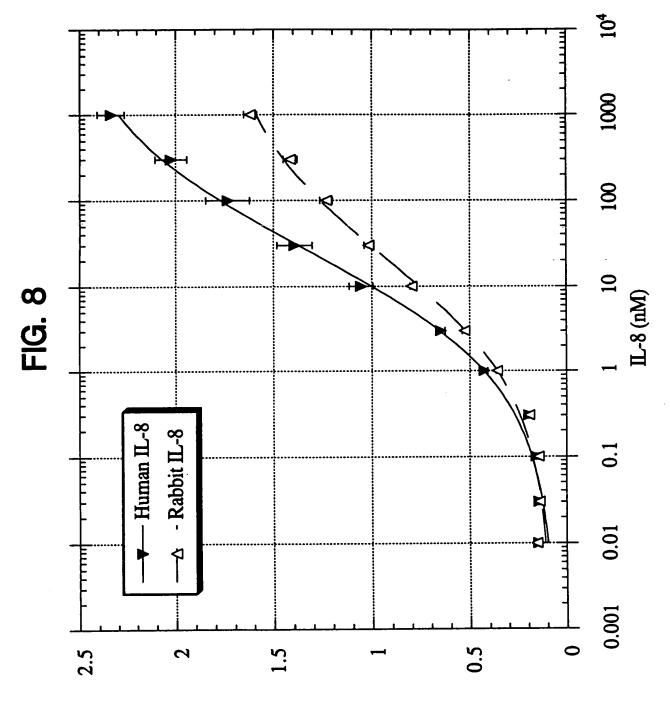


FIG. 7

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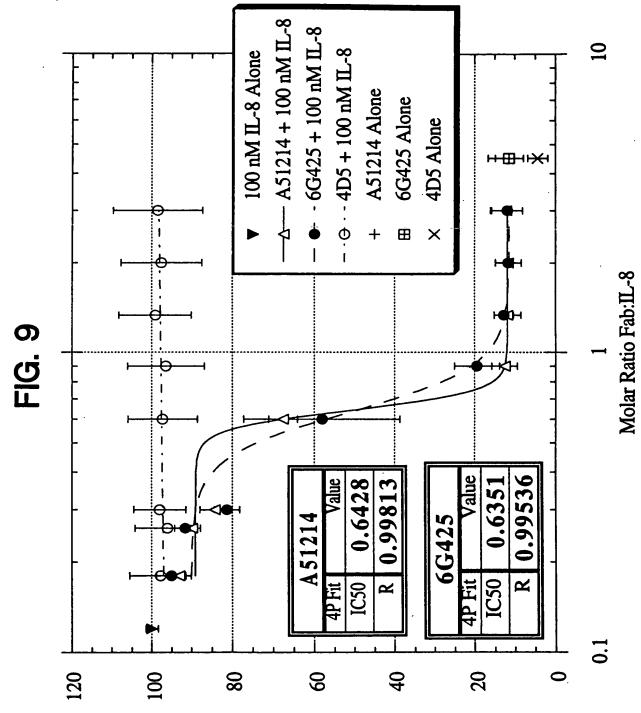


Absorbance (405 nm)

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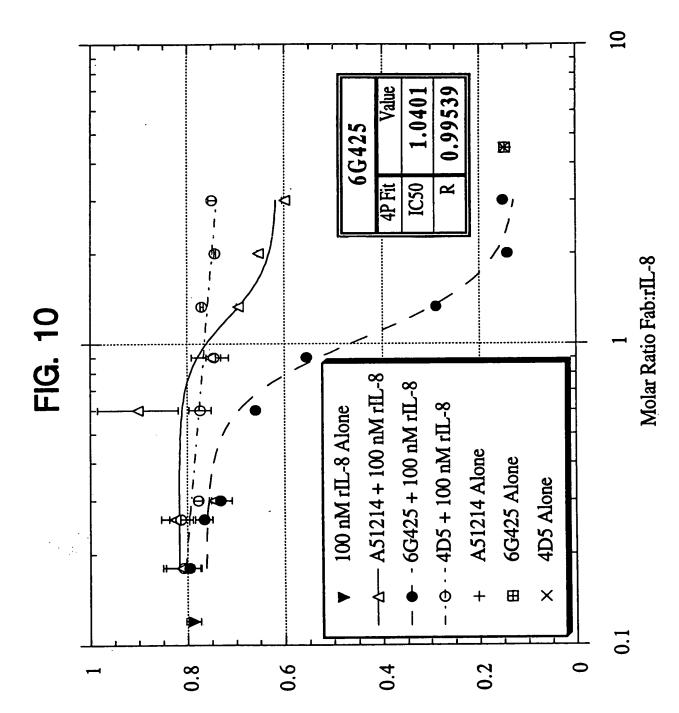




% IL-8-Stimulated Elastase Release

ANTIBODY FRAGMENT-POLYMER CONJUGATES AND HUMANIZED
ANTI-IL-8 MONOCLONAL ANTIBODIES
Hsei et al.

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Absorbance (405 nm)

OT PE VOIS

ANTIBODY FRAGMENT-POLYMER CONJUGATES AND HUMANIZED ANTI-IL-8 MONOCLONAL ANTIBODIES Hsei et al. Atty Docket: GENENT.093A Appl. No.: 09/234,182 OCT 2 1 2002 17 mg/mL TNBS n=5 iv anti-IL-8 FIG. 11B 17 mg/mL TNBS n=14 iv saline **1**-8 Untreated 91 \$ \$ 8 \$ pg/mg Tissue (mean±SEM) 17 mg/mL TNBS n=5 iv anti-IL-8 **MYELOPEROXIDASE** FIG. 11A 17 mg/mL TNBS n=14 iv saline Untreated 8 ė 9 8 ß \$ ဒ္က mOD/minute (mean±SEM)

ANTIBODY FRAGMENT-POLYMER CONJUGATES AND HUMANIZED ANTI-IL-8 MONOCLONAL ANTIBODIES Hsei et al. Atty Docket: GENENT.093A Appl. No.: 09/234,182 OCT 2 1 2002 17 mg/mL TNBS n=5 iv anti-IL-8 GROSS INFLAMMATION FIG. 11D 17 mg/ml TNBS n=14 iv saline Untreated 9 င္တ \$ င္က Ŕ ė (GS±nsem) DUA 17 mg/mL TNBS n=5 iv anti-IL-8 **COLON WEIGHT** FIG. 11C 17 mg/mL TNBS n=14 iv saline Untreated Ą mg/cm/kg Body Weight mean±SD উ ই Š 8

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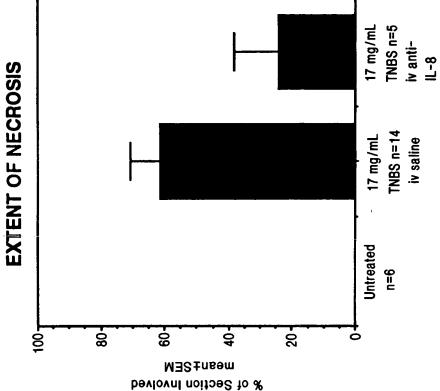
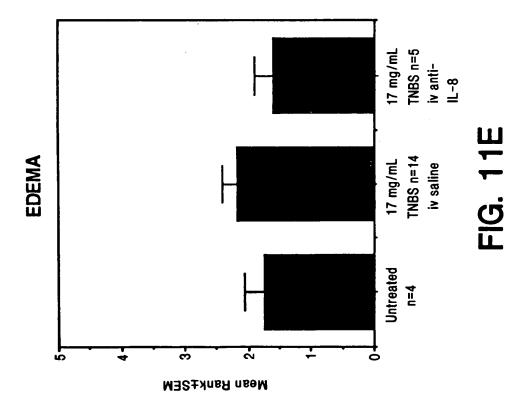


FIG. 11F



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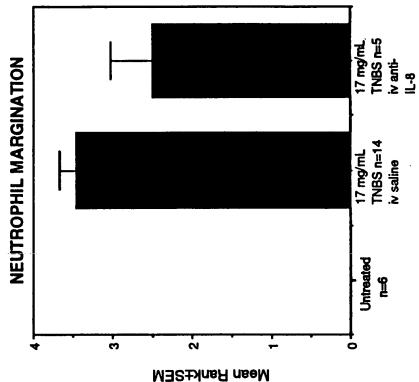


FIG. 11H

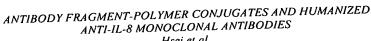
FIG. 11G

SEVERITY OF NECROSIS

Severity of Necrosis

Severity of Necrosis

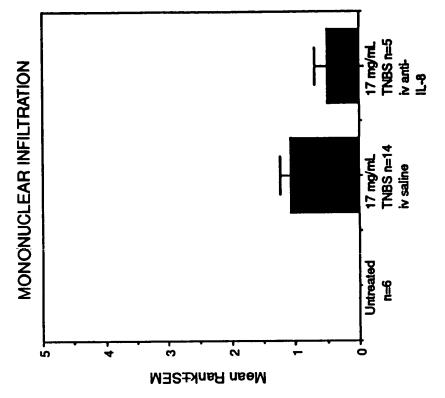
Outreated 17 mg/mL 17 mg/mL

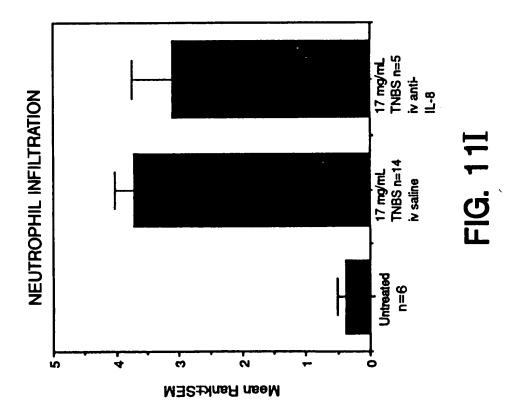


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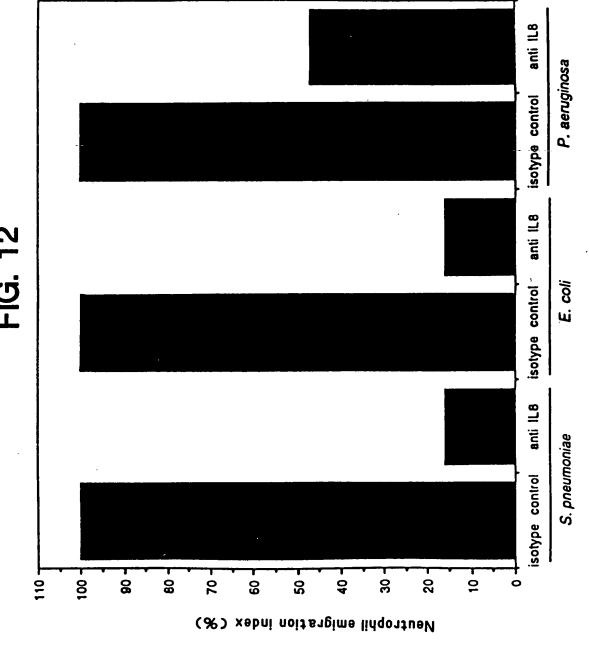






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Group (n=5 rabbits per group)



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Light Chain Primers:

MKLC-1, 22mer

FIG. 13

5' CAGTCCAACTGTTCAGGACGCC 3' (SEQ ID NO.1)

MKLC-2, 22mer

5' GTGCTGCTCATGCTGTAGGTGC 3'(SEQ ID NO.2)

MKLC-3, 23mer

5' GAAGTTGATGTCTTGTGAGTGGC 3'(SEQ ID NO.3)

Heavy Chain Primers:

IGG2AC-1, 24mer

5' GCATCCTAGAGTCACCGAGGAGCC 3'(SEQ ID NO.4)

IGG2AC-2, 22mer

CACTGGCTCAGGGAAATAACCC 3 '(SEQ ID NO.5)

IGG2AC-3, 22mer

5' GGAGAGCTGGGAAGGTGTGCAC 3' (SEQ ID NO.6)



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Light chain forward primer

35 mer SL001A-2 3 ' (SEQ ID NO.7) (SEQ ID NO.8) (SEQ ID NO.9) 5' ACAAACGCGTACGCT GACATCGTCATGACCCAGTC

HA

Light chain reverse primer

37 mer

SL001B

5' GCTCTTCGAATG GTGGGAAGATGGATACAGTTGGTGC 3'(SEQ ID NO.10)



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(SEQ ID NO.14)

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Heavy chain forward primer

mer

39

SL002B

5' CGATGGCCCGG ATAGACCGATGGGCCTGTTGTTTGGC 3' (SEQ ID NO.11)
T
C (SEQ ID NO.12)
G

H U A

Heavy chain reverse primer

39-MER SL002B 5' CGATGGGCCCGG ATAGACCGATGGGGCTGTTTTGGC

H A U

3 ' (SEQ ID NO.11) (SEQ ID NO.15) (SEQ ID NO.14) (SEQ ID NO.13)



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CAGGGTCAGC GTCCCAGTCG ACAGAAACCA TGTCTTTGGT > 民 CCTGGTATCA GACATTGTCA TGACACAGTC TCAAAAATTC ATGTCCACAT CAGTAGGAGA GGACCATAGT TACAGGTGTA GTCATCCTCT > GAATGTGGGT ACTAATGTAG CTTACACCCA TGATTACATC ഗ ഗ AGTTTTTAAG ĸ Ø CTGTAACAGT ACTGTGTCAG GTCACCTGCA AGGCCAGTCA CAGTGGACGT TCCGGTCAGT >

Ø 3 Ŋ CDR #1 d Ø ပ E > 61

AGTCCCTGAT GATTTACTCG TCATCCTACC GGTACAGTGG CCATGICACC ß CTAAATGAGC AGTAGGATGG * Н 121 GGGCAATCTC CTAAAGCACT GATTTCGTGA ø × CCCGTTAGAG ഗ Ø

CDR #2

ACACGTCAGA TGTGCAGTCT CGCTTCACAG GCAGTGGATC TGGGACAGAT TTCACTCTCA CCATGAGCCA ACCCTGTCTA AAGTGAGAGT GGTAGTCGGT ഗ Ы E Œ Ω E ტ CGTCACCTAG G ഗ GCGAAGTGTC

CAAGCCAGGA GTTCGGTCCT TATAACATCT ATCCTCTCAC ATATTGTAGA TAGGAGAGTG ы CTGTCAGCAA GACAGTCGTT Ø ပ GAAGACTTGG CAGACTATTT GTCTGATAAA CTTCTGAACC Ω 241

CATCTTCCCA GTAGAAGGGT GGGACCAAGC TGGAGTTGAA ACGGGCTGAT GCTGCACCAC CAACTGTATC TGCCCGACTA CGACGTGGTG GTTGACATAG Д **V** ¥ Ø 召 CCCTGGTTCG ACCTCAACTT 回 G 301 101

BstBI

361 CCA*TTCGAA* (SEQ ID NO.16) GGT*AAGCTT* 121 *P F E* (SEQ ID NO.17)

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ANTIBODY FRAGMENT-POLYMER CONJUGATES AND HUMANIZED ANTI-IL-8 MONOCLONAL ANTIBODIES

Hsei et al.
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1 TTCTATTGCT ACAAACGCGT ACGCTGAGGT GCAGCTGGTG GAGTCTGGGG GAGGCTTAGT AAGATAACGA TGTTTGCGCA TGCGACTCCA CGTCGACCAC CTCAGACCCC CTCCGAATCA OLV E S G G GLV E V 61 GCCGCCTGGA GGGTCCCTGA AACTCTCCTG TGCAGCCTCT GGATTCATAT TCAGTAGTTA CGGCGGACCT CCCAGGGACT TTGAGAGGAC ACGTCGGAGA CCTAAGTATA AGTCATCAAT G F I F S S Y L S C A A S 13 P P G G S L K **CDR #1** 121 TGGCATGTCT TGGGTTCGCC AGACTCCAGG CAAGAGCCTG GAGTTGGTCG CAACCATTAA ACCGTACAGA ACCCAAGCGG TCTGAGGTCC GTTCTCGGAC CTCAACCAGC GTTGGTAATT T P G K S L ELVA WVRQ 33 G M S 181 TAATAATGGT GATAGCACCT ATTATCCAGA CAGTGTGAAG GGCCGATTCA CCATCTCCCG ATTATTACCA CTATCGTGGA TAATAGGTCT GTCACACTTC CCGGCTAAGT GGTAGAGGGC G R F T Y P D s v K I S R **CDR #2** 241 AGACAATGCC AAGAACACCC TGTACCTGCA AATGAGCAGT CTGAAGTCTG AGGACACAGC TCTGTTACGG TTCTTGTGGG ACATGGACGT TTACTCGTCA GACTTCAGAC TCCTGTGTCG KNTL Y L Q M S S LKSE 73 D N A Y Т G 93 M F Y CAR Α S W F **CDR #3** 361 AGGGACTCTG GTCACTGTCT CTGCAGCCAA AACAACAGCC CCATCTGTCT TCCCTGAGAC CAGTGACAGA GACGTCGGTT TTGTTGTCGG GGTAGACAGA PSVY 113 G T L V T V S A A K TTA ApaI ATCCGGG (SEO ID NO.18) 411 TAGGCCC **FIG. 17** (SEQ ID NO.19) 130 P



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FIG. 18

VL.front 31-MER

5 ' ACAA<u>ACGCGT</u>ACGCT<u>GATATC</u>GTCATGACAG 3 ' (SEQ ID NO.20)

VL.rear 31-MER

5' GCAGCATCAGCTCTTCGAAGCTCCAGCTTGG 3'(SEQ ID NO.21)

VH.front.SPE 21-MER

5' CCACTAGTACGCAAGTTCACG 3'(SEQ ID NO.22)

VH.rear 33-MER

5' GATGGGCCCTTGGTGGAGGCTGCAGAGACAGTG 3' (SEQ ID NO.23)

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61				CGTCAT GCAGTA												
-3	A Y			V M		Q				F M	S		s	V		
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241				CACAGG GTGTCC												
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90	AAGCC		CCTG	GTTCGA K L		CGAA L				ACACC V A		TGGT. P			BAAG F	
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421				TGAGCA ACTCGT												
118				E Q												
481			_	AGAGGC												
138				TCTCCG E A												
2#1				TGTCAC ACAGTG												
158	N S	Q E	S	V T	E	Q	D	S	K	D S	T	Y	S ,	L	S	S
601				CAAAGC												
178				GTTTCG KA							_		_			
661				CTCGCC												
198				GAGCGG S P						STTGT N R				EO I	D N	O 251
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419	0															

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				СT	TATA															
-23	M	K	K	N	Ι	A	F	L	L	A	S	M	F	V	F	S	I	A	T	N
61					AGGT TCCA															
-3	A					Q			E	S	G			L		P		G	G	S
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121					CCTG															
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181					CAGG															
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241					CAGA															
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301					ACGT															
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361	AGA	GCC	ст	CA	TTAG	TTC	GC	TAC	TTG	GTTT	GG'	TTA(CTG	GG	GCCA	AGG	GAC	TCT	GGT	САСТ
					AATC															
98	R	Α	<u>L</u>	I	S	S	<u> A</u>	T	W	F_	G	Y	W	G	Q	G	${f T}$	L	V	T
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421					GGAG															
118	V	S	A	A	S	T	K	G	P	S	V	F	P	L	A	P	S	S	K	S
481	ACC	ייייי	rgge	GG	GCAC.	AGC	GGC	ССТ	GGG	CTGC	СТ	GGT	CAA	.GG	АСТА	CTT	CCC	CGA	ACC	GTG
	TGG	AG/	ACC	CC	CGTG	TCG	CCG	GGA	CCC	GACG	GA	CCA	GTT	CC	TGAT	GAA	GGG	GCT'	TGG	CCAC
138	T	S	G	G	T	A	A	L	G	C	L	V	K	D	Y	F	P	E	P	V
541					GGAA															
					CCTT															
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601					GACT															
450					CTGA															
178	Q	S	S	G	L	Y	S							V	P	5	3	5	ப	G
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FIG. 20A



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> 661 ACCCAGACCT ACATCTGCAA CGTGAATCAC AAGCCCAGCA ACACCAAGGT GGACAAGAAA CCTGTTCTTT TICGGGICGT TGTGGTICCA GCACTTAGTG TGGGTCTGGA TGTAGACGTT

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(SEQ ID N0.26) 721

GTTGAGCCCA AATCTTGTGA CAAAACTCAC ACATGA CAACTCGGGT TTAGAACACT GTTTTGAGTG TGTACT V E P K S C D K T H T O T H ပ Ŋ Ø > 218

(SEQ ID NO.27)

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ANTIBODY FRAGMENT-POLYMER CONJUGATES AND HUMANIZED ANTI-IL-8 MONOCLONAL ANTIBODIES

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Light Chain Primers:

MKLC-1, 22mer

5' CAGTCCAACTGTTCAGGACGCC 3' (SEQ ID NO.1)

MKLC-2, 22mer

5' GTGCTGCTCATGCTGTAGGTGC 3' (SEQ ID NO.2)

MKLC-3, 23mer

5' GAAGTTGATGTCTTGTGAGTGGC 3' (SEQ ID NO.3)

Heavy Chain Primers:

IGG2AC-1, 24mer

5' GCATCCTAGAGTCACCGAGGAGCC 3' (SEQ ID NO.4)

IGG2AC-2, 22mer

5' CACTGGCTCAGGGAAATAACCC 3' (SEQ ID NO.5)

IGG2AC-3, 22mer

5' GGAGAGCTGGGAAGGTGTGCAC 3' (SEQ ID NO.6)

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Light chain forward primer

36-MER 6G4.light.Nsi 3 ' (SEQ ID NO.28) (SEQ ID NO.29) (SEQ ID NO.30) 5' CCAATGCATACGCT GAC ATC GTG ATG ACC CAG ACC CC
T T T T T A A A A

Light chain reverse primer

35-MER 6G4.light.Mun 5' AGA TGT CAA TTG CTC ACT GGA TGG TGG GAA GAT GG 3' (SEQ ID NO.31)

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Heavy chain forward primer

6G4.heavy.Mlu 32-MER

3 · (SEQ ID NO.32) (SEQ ID NO.33) 5' CAAACGCGTACGCT GAG ATC CAG CTG CAG CAG
T C

Heavy chain reverse primer

39-MER

SL002B

3 ' (SEQ ID NO.11) (SEQ ID NO.15) (SEQ ID NO.14) (SEQ ID NO.13) 5' CGATGGCCCGG ATAGACCGATGGGGCTGTTTTTGGC E A U

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ANTIBODY FRAGMENT-POLYMER CONJUGATES AND HUMANIZED ANTI-IL-8 MONOCLONAL ANTIBODIES

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70 G ATATCGTGAT GACACAGACA CCACTCTCCC TGCCTGTCAG TCTTGGAGAT C TATAGCACTA CTGTGTCTGT GGTGAGAGGG ACGGACAGTC AGAACCTCTA D I V M T Q T P L S L PVS 121 CAGGCCTCCA TCTCTTGCAG ATCTAGTCAG AGCCTTGTAC ACGGTATTGG AAACACCTAT GTCCGGAGGT AGAGAACGTC TAGATCAGTC TCGGAACATG TGCCATAACC TTTGTGGATA S C R S S Q SLVHGI G_ N 18 Q A S I ☆ A * * * * **CDR #1** 181 TTACATTGGT ACCTGCAGAA GCCAGGCCAG TCTCCAAAGC TCCTGATCTA CAAAGTTTCC AATGTAACCA TGGACGTCTT CGGTCCGGTC AGAGGTTTCG AGGACTAGAT GTTTCAAAGG 38 L H W Y L Q K P G Q SPKL LI K V S CDR #2 241 AACCGATTTT CTGGGGTCCC AGACAGGTTC AGTGGCAGTG GATCAGGGAC AGATTTCACA TTGGCTAAAA GACCCCAGGG TCTGTCCAAG TCACCGTCAC CTAGTCCCTG TCTAAAGTGT 58 N R F S G V P D R F S G S G SGT 301 CTCAGGATCA GCAGAGTGGA GGCTGAGGAT CTGGGACTTT ATTTCTGCTC TCAAAGTACA GAGTCCTAGT CGTCTCACCT CCGACTCCTA GACCCTGAAA TAAAGACGAG AGTTTCATGT LGLY F C 78 L R I S R V E A E D QST CDR #3 361 CATGTTCCGC TCACGTTCGG TGCTGGGACC AAGCTGGAGC TGAAACGGGC TGATGCTGCA GTACAAGGCG AGTGCAAGCC ACGACCCTGG TTCGACCTCG ACTTTGCCCG ACTACGACGT AGTKLEL TFG K R A D A A 98 <u>H V P L</u> MunI 421 CCAACTGTAT CCATCTTCCC ACCATCCAGT GAGCAATTGA (SEO ID NO.34) GGTTGACATA GGTAGAAGGG TGGTAGGTCA CTCGTTAACT PSSEQLK (SEQ ID NO.35) 118 P T V S I F P

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				ATA	GG	ACGT	TCCG	AAG	ACC	ATAA:	AC	STAA	GTC	CAT							
18	V	K	I	S	C	C K	A	S	G	<u>Y</u>	S	F	S	<u>S</u>		1 '	(M	Н	W	V
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181	AA	GCA	GAC	CC	ATC	GAA	AGAG	CCI	TGA	GTGG	ľĀ	rtgg	CTA	ACA	TTC	TAE	CI	TC	CAA	TGC	TGAA
	ТТ	CGT	CTC	CGG	TAC	יתיים:	TCTC	GGA	ACT	CACC	ጥል	ACC	'GA'	ጥርሃገ	AAC	מתי	()	DA	СТТ	יא כיכ	יעריטעי
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241	AC	'TAC	TTA	CA	ACC	AGA	TTAA	CAA	GGG	CAAG	GC	CAC	'ATI	'GA	СТС	TAC	AC	'AC	ATC	ттс	CAGC
	TG	ATG	RAT	GT	TGG	TCT	ТТАА	GTT	CCC	GTTC	CC	CTC	ממיד	СТ	GAC	י א ייר	יתיכ	TC:	TAG	ΔΔα	CTCC
58		т	Y	N	C		F	K	G	K	A		L	Т	V			т	S	S	S
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301	AC	AGC	CAA	CG	TGC	'ATC	TCAG	CAG	CCT	GACA	TC	TGA	TGA	CT	CTG	CAG	TC	TA	ттт	CTG	TGCA
	TG	TCG	GTI	CGC	ACG	TAG	AGTC	GTC	GGA	CTGT	AG	ACT	ACI	'GA	GAC	GTC	'AG	AT	AAA	GAC	ACGT
78	T	Α	N	V	Н	L	S	S	L	T	S	D	D	S	А	v	,	Y	F	С	A
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361										CTGG											
	TC	TCC	CCI	'GA	TAT	CTA?	rgtt	GCC	GCT	GACC	AA	AAA	GCI	'AC	AGA	CCC	CG	CG	TCC	CTG	GTGC
98	R	G	<u>D</u>	_Y	R	Y	N	G	D	W	F	F	D	V	W	G	}	Α	G	T	'n
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	В	stE:	ΙΙ														Ap	aΙ			
421	GT	'CAC	CGT	CT	CCT	CCGC	CCAA	AAC	CGA	CAGC	CC	CAT	CGG	TC	TAT	CCG	GG	CC			
										GTCG											
118				S		Α		T	D	S	P		G	L	S		-	P			
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471		ATC AG	(2)	ĽŲ I	א עו	O .36)														
135	I		(SI	EO I	ID N	O.37)														
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Appl. No.: 09/234,182 Atty Docket: GENENT.093A

5' CTTGGTGGAGGCGGAGGAGACG 3' (SEQ ID NO.38)

Mutagenesis Primer for 6G425VL

DS/VF 38MER

5' GAAACGGGCTGTTGCTGCACCAACTGTATTCATCTTCC 3'(SEQ ID NO.39)

SYN.BstEII 31 MER

5' GTCACCGTCT CCTCCGCCTC CACCAAGGGC C 3' (SEQ ID NO.40)

SYN.Apa 22 MER

5' CTTGGTGGAGGCGGAGGAGACG 3' (SEQ ID NO.38)

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1					ATAT TATA															
-23	M	K	K	N	I	A	F	L	L	A	S	M	F	V	F	S	I	A	T	N
61					ATAT TATA															
-3	A	Y	A	D	I	V	M	T	Q	T	P	L	S	L	P	V	S	L	G	D
121					TCTC															
18	Q.	A	S	I	S	C	R	S	S	0	S	L	V	H	G	_I_	G	N	ፗ	X
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181					ACCT TGGA															
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241					CTGG															
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301					GCAG											*. \				
78	L			S		V		A		D		G			F	C	S	0	S	T
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361					TCAC AGTG												CI GGC:	OR #	rgc	IGCA
361 98	GTA							ACG	ACC		TTC	CGAC	CTC	CG	ACTT		CI GGC CCG	TGT ACA	rgc	rgca Acgt
	GTA	CAA				CAA	GCC	ACG	ACC	CTGG	TTC	CGAC	CTC	CG	ACTT	TGC	CI GGC CCG	TGT ACA	rgc: Acg/	rgca Acgt
98	GTAG	CAA V * ACT	GGC P *	G L *	AGTG T *	CAA(F	GCC G CCC	ACC	ACC(G ATC(T T CAGT	TTO K	CGAC L SCAA	CCT(E ATT(CG L GA	ACTT K AATC	TGC R TGG	CI GGC CCG A A	TGC	TGC! ACG! A	IGCA ACGT A
98	GTAG	CAA V * ACT TGA	GGC P * * * * *	G L * T	AGTG T * TCAT AGTA	CAAC F CTTC	GCC G CCC GGG	ACGA A ACCA TGG	ACC(G ATC(FAG(TTGG T CAGT GTCA	TTO K GAO CTO	CGAC L GCAA CGTT	CCTC E ATTC TAAC	CG L GA CT	ACTT K AATC TTAG	TGC R TGG	CI GGC CCG A AAC TTG	TGT' ACA TGC ACG	TGC: ACGA A CTC:	IGCA ACGT A IGTT ACAA
98 421 118	GTAC H '	CAA V * ACI TGA	GGC * * * * * * * * * * * * * * * * * * *	G L T T A F	AGTG T * TCAT AGTA I	CAA(F CTT(GAA(F	GCC G CCC GGG P	ACCA TGG	ACC(G ATC(FAG(S	CTGG T CAGT GTCA S	TTO K GAO CTO E	CGAC L GCAA CGTT	E E ATT(PAA(L	CG L GA CT K	ACTT K AATC TTAG	TGC R TGG ACC G	GGC CCG A AAC TTG T	TGT' ACAL V TGCG ACGG	PGC: ACG: A CTC: GAG:	IGCA ACGT A IGTT ACAA V
98 421 118	GTAG	CAA V * ACI TGA T	GGC # * GTA CAT V	G L * TAF	AGTG TCAT AGTA I TGAA	CAAC F CTTC GAAC F	GCC G CCC GGG P	ACGA ACCA TGGA P	ACCO G ATCO FAGO S	CTGG T CAGT GTCA S CAGA	TTO K GAO CTO E	CGAC L ECAL CGT1 Q	E ATTO	GA CT K	ACTT K AATC TTAG S TACA	TGC R TGG ACC G	GGC A AAC TTG T	TGT ACAL V TGCO ACGO A	TGC'ACGA	IGCA ACGT A IGTT ACAA V
98 421 118 481	GTAGGTTP	CAA V * ACT TGA TGC ACG	GGC * * * * * * * * * * * * * * * * * *	G L * TAF GG	AGTG T * TCAT AGTA I TGAA ACTT	CAAC F CTTC GAAC F TAAC	GCC GCC GGG P	ACCATGG	ACCO G ATCO IAGO F CCO AGGO	CTGG T CAGT GTCA S CAGA GTCT	GAG GAG CTG E	EGAC EGTT Q EGCC	ECTO E ATTO FAAO L CAAO	GA CT K AG	ACTT K AATC TTAG S TACA ATGT	TGC R TGG ACC G GTG	GGC CCG A AAC TTG T GAA CTT	TGT ACAL ACG ACG ACG CCA	TGCTACGACTACACACTACACACTACACACTACACACTACACACAC	IGCA ACGT A IGTT ACAA V IAAC ATTG
98 421 118 481 138	GTAGGGTGCAC	CAA Y * ACI IGA T	GGC * * * * * * * * * * * * * * * * * *	CG L * TAF CCG L	AGTG T * TCAT AGTA I TGAA ACTT N	CAAC F CTTC GAAC F TAAC VATTC	GCC G CCC GGG P CTT GAA F	ACGA ACCA TGG' P CTA' GATA	ACCO G ATCO F ICCO AGGO	CTGG T CAGT GTCA S CAGA GTCT R	TTO K GAO CTO E GAO CTO	EGAC L EGTT Q EGCC EGCC	CCTO E ATTO FAAO L CAAD STTT	GA GA CT K AG IC	ACTT K AATC TTAG S TACA ATGT	TGC R TGG ACC G GTG CAC	GGC CCG A AAC TTG T GAA CTT	TGT'ACA	TGCTACGAGAGAGAGAGAGAGAGAGAGAGAGAGAGAGAGA	IGCA ACGT A IGTT ACAA V IAAC ATTG
98 421 118 481 138	GTAGGGTGCAC	CAA Y * ACI TGA TGC ACC	GGC	CGL * TAF CCGL	AGTG T * TCAT AGTA I TGAA ACTT N CGGG	CAAC F CTTC GAAC F TAAC ATTC	GCC GCC GGG P CTT GAA F	ACGA A ACCA TGG TGG P CTA GATA Y CCA	ACCO G ATCO P CGAO	CAGT GTCA S CAGA GTCT R GAGT	GAG CTG E GAG CTG E	EGAC	CCTO E ATTO PAAC L CAAC GTTO K	CG L GA CT K AG IC V	ACTT K AATC TTAG S TACA ATGT Q AGGA	TGC R TGG. ACC G GTG CAC W	GGC CCG A AAC TTG T GAA CTT K	TGT'ACA	TGCTACGAGAGAGAGAGAGAGAGAGAGAGAGAGAGAGAGA	IGCA ACGT A IGTT ACAA V IAAC ATTG N
98 421 118 481 138 541	GTAGGGTGCACACACACACACACACACACACACACACACA	CAA V * ACT TGA TGC CTC GAG	GGC	CG L * TAF CCG L TA	AGTG T * TCAT AGTA I TGAA ACTT N CGGG GCCC	CAAC F CTTC GAAC F TAAC ATTC	GCC GCC GGG P CTT GAA F	ACGA A ACCA TGG' P CTA' GATA Y CCAC GGTC	ACCO G ATCO F P AGGO P GGAO	CAGT GAGA GAGA GAGA GAGA GAGA GAGA GAGA	GAG CTC E GAG CTC E	GGAC GCAA GGTT Q GCCGC A CAC GTGT	CCTO E ATTO PAAC L CAAC STTT K	CG L GA CT K AG IC V	ACTT K AATC TTAG S TACA ATGT Q AGGA TCCT	TGC R TGG. ACC G GTG CAC	GGC CCG A AAC TTG T GAA CTT K	TGT'ACA' V TGC'ACG'ACG'A' GGT'CCA' V GGA'CCT'CCT'CCT'CCT'CCT'CCT'CCT'CCT'CCT'CC	TGCTACGACGACGACGACGACGACGACGACGACGACGACGACGA	IGCA ACGT A IGTT ACAA V IAAC ATTG N
98 421 118 481 138 541 158	GTAGGGT' P GTG' CACCCGGGA	CAA V * ACT TGA TGA CGACG CTC GAG	GGGC P * * * * * * * * * * * * * * * * * *	GL* TAF CGL TAS	AGTG T * TCAT AGTA I TGAA ACTT N CGGG GCCC G	CAAC F CATTO GAAC TAAC ATTO N	GCC G G GGG P CTT GAA F CTC GAG	ACGA A ACCA TGG' P CTA' GATA Y CCAC GGTC Q	ACCO G ATCO P AGGO P GGAO CCTO	CAGT GTCA S CAGA GTCT R GAGT CTCA S	GAG CTC E GAG CTC E	EGAC L EGTT Q EGCC CCGC A EACA EACA	E ATTY PAAG L CAAA K AGAG CTY E	GG L GA CT K AG IC V GC Q	ACTT K AATC TTAG S TACA ATGT Q AGGA TCCT D	TGC R TGG. ACC G GTG CAC W	GGC CCG A AAC TTG T GAA CTT K	TGT ACAL V TGCO ACGO A GGTO CCAC V GGAO CCTO D	TGCTACGACGACGACGACGACGACGACGACGACGACGACGACGA	IGCA ACGT A IGTT ACAA V IAAC ATTG N CACC GTGG
98 421 118 481 138 541 158	GTAGGGT'PGTAGGGT'A	CAAAV * ACT TGA CC CTC GAC GAC AGC AGC AGC AGC AGC AGC AGC AG	GGGC P * * * * * * * * * * * * * * * * * *	GL* TAF CGL TAS A	AGTG T * TCAT AGTA I TGAA ACTT N CGGG GCCC G	CAAC F CATC GAAC ATTC N CATC	CCC GGG P CTT GAA F CTC GAG	ACCA ACCA TGG' P CTA' GATA Y CCAC GGTC Q	ACCC G ATCC P AGGC P GGAC CCTC	CAGT GTCA S CAGA GTCT R GAGT CTCA S GAGT GAGT GAGT GAGT GAGT GAGT GAGT G	GAG CTC E GAG CTC E	EGAC L EGTT Q EGCC A EAC T	E ATTY PAAG L CAAA K AGAG PCTG E	GG L GA CT K AG IC V GC GC Q CT	ACTT K AATC TTAG S TACA ATGT Q AGGA TCCT D	TGC R TGG ACC G GTG CAC W .CAG GTC	GGC CCG A AAC TTG T GAA CTT K CAA GTT K	TGT ACAL ACGO ACGO ACGO CCAC CCTC D	PGCTACGACGACGACGACGACGACGACGACGACGACGACGACGA	IGCA ACGT A IGTT ACAA V IAAC ATTG N CACC GTGG T
98 421 118 481 138 541 158 601	GTAGGGT'PGTAGGGT'A	CAAAV * ACT TGA CC CTC GAG AGC TTC CTC CTC CTC CTC CTC CTC CTC CTC C	GGGC P * * * * * * * * * * * * * * * * * *	GL * TAF CGL TAS AT	AGTG T TCAT AGTA I TGAA ACTT N CGGG GCCC G GCAG CGTC	CAAC F CTTC GAAC F TAAC ATTC N CATTC	GCC GCC GGG P CTT GAA F CTC GAG S	ACGA A ACCA TGGT P CTA GATA Y CCAC GGTC Q GACC CTGC	ACCC G ATCC P AGGC P GGAC E GCTC	CTGG T CAGT GTCA S CAGA GTCT R GAGT CTCA S GAGC CTCG	GAGCTC E GTGC V AAA	GGAC GCAA GGCC A CACA T AGCA	E ATTY PAAC L CAAL K AGAC CCT E	GA CT K AG IC V GC GC Q CT GA	ACTT K AATC TTAG S TACA ATGT Q AGGA TCCT D ACGA TGCT	TGC R TGG ACC G GTG CAC W CAG CTC	GGC CCG A AAC TTG T GAA CTT K CAA GTT K	TGT ACAL ACGO ACGO ACGO CCAA CCCT CC	TGCTAGAGAGAGAGAGAGAGAGAGAGAGAGAGAGAGAGAG	IGCA ACGT A IGTT ACAA V IAAC ATTG N CACC ETGG T CTAC
98 421 118 481 138 541 158 601	GTAGGGT'PGTAGGGT'A	CAAAV * ACT TGA CC CTC GAG AGC TTC CTC CTC CTC CTC CTC CTC CTC CTC C	GGGC P * * * * * * * * * * * * * * * * * *	GL * TAF CGL TAS AT	AGTG T * TCAT AGTA I TGAA ACTT N CGGG GCCC G	CAAC F CTTC GAAC F TAAC ATTC N CATTC	GCC GCC GGG P CTT GAA F CTC GAG S	ACGA A ACCA TGG' P CTA' GATA Y CCAC GGTC Q GACC CTGC	ACCO G ATCO IAGO P GGAO CCTO E	CTGG T CAGT GTCA S CAGA GTCT R GAGT CTCA S GAGC CTCG	GAG CTC E GAG CTC E GTC CAG V	EGAC L EGCT Q EGCC CCGC A EACA EACA EACA EACA EACA EA	E ATTY PAAG L CAAA K AGAG CTY E	GA CT K AG IC V GC GC Q CT GA	ACTT K AATC TTAG S TACA ATGT Q AGGA TCCT D ACGA TGCT	TGC R TGG ACC G GTG CAC W CAG CTC	GGC CCG A AAC TTG T GAA CTT K CAA GTT K	TGT ACAL ACGO ACGO ACGO CCAA CCCT CC	TGCTAGAGAGAGAGAGAGAGAGAGAGAGAGAGAGAGAGAG	IGCA ACGT A IGTT ACAA V IAAC ATTG N CACC ETGG T CTAC



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> 661 GCCTGCGAAG TCACCCATCA GGGCCTGAGC TCGCCCGTCA CAAAGAGCTT CAACAGGGGA GTTGTCCCCT CCCGGACTCG AGCGGGCAGT GTTTCTCGAA

Ŋ ტ CGGACGCTTC AGTGGGTAGT 囡

198

(SEQ ID NO.41) 721 GAGTGTTAA

(SEQ ID NO.42) CTCACAATT 0 Ü E4 218

FIG. 27B

OCT 2 1 2002

ANTIBODY FRAGMENT-POLYMER CONJUGATES AND HUMANIZED ANTI-IL-8 MONOCLONAL ANTIBODIES Hsei et al.

Appl. No.: 09/234,182 Atty Docket: GENENT.093A

1					TATA															
					TATA											_			_	
-23	M	K	K	N	I	A	F	L	L	A	S	M	F	V	F	S	Ι	A	T	'N
61					AGAT															
	CG	CAT	GCG	AC	ТСТА	AGT	CGA	CGT	CGT	CAGA	CC	TGG.	ACT	CG.	ACTA	CTT	CGG	ACC	CCG.	AAGT
-3	A	Y	A	E	I	Q	L	Q	Q	S	G	P	E	L	M	K	P	G	A	S
121					CCTG															
10		K				K										GAT Y	GTA M	H	GAC W	
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181	AA	CCAC	GAG	CC	ATGG	AAA	SAG	CCT	TCA	CACC	AΤ	ጥርር	СТА	CA	ጥጥረል	ጥርር	THE THE	CAA	TCC	TY2A A
					TACC															
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241					ACCA TGGT															
58		MIG2 ጥ	Y	N		K	F	K		K					GACA V					
56	.t	1	I #	7. 7.4	Q	* V	r t		G	K	A	T	L	T	V	D	T	S	S	S
	¥	¥	ਸ	ਸ	¥	ਸ	¥	*	Ħ											
301	AC	AGC(CAA	CG	TGCA	TCT	CAG	CAG	CCT	GACA	TC:	TGA'	IGA	СТ	CTGC.	AGT	СТА	TTT	CTG'	TGCA
	TG'	TCG(3TT	GC	ACGT	AGA(GTC	GTC	GGA (CTGT	AG	ACT	ACT	GA	GACG	TCA	GAT	AAA	GAC	ACGT
78	T	Α	N	V	Н	L	S	S	L	T	S	D	D	S	A	V	Y	F	С	A
361	AG	AGG	3GA	СТ	ATAG	АТАС	CAA	CGGG	CGAC	TTGG	тт	ኮጥጥ	CGA	TG	ጥርጥር	GGG	CGC	AGGG	SACO	~ACG
					TATC															
98		G					N		D	W	F		D	v	W			G		т
		*	*	#	*	*	A	*	*	A	*	*	*	*				_	_	-
						CDF	R #3	1												
421					CCTC															
	CAC				GGAG															
118	V	${f T}$	V	S	S	A	S	$oldsymbol{T}$	K	G	P	S	V	F	P	$oldsymbol{L}$	A	P	S	S
481	AAC	GAGC	CAC	CT	CTGG	GGGC	CAC	·AGCC	GCC	CTG	GG	CTG	CTY	GG	TCAA	GGA	CTA	CTTC	CCC	CGAA
	TTC	CTCC	TG(GΑ	GACC	CCCG	FTG	TCGC	CCGC	GAC	CCC	GACC	GA (CC	AGTT	CCT	GAT	GAAC	GGG	CTT
138	K	S	T	S	G	G	T	A	A	$oldsymbol{L}$	G	C	L	V	K	D	Y	F	P	E
541	CCC	3GTC	BAC	3G	TGTC	GTGC	AA	CTCA	AGGC	CGCC	CTC	GACC	CAG	CG	GCGT	GCA(CAC	CTTC	CCC	GCT
					ACAG										CGCA	CGTY	GTG	GAAC	GGG	CCGA
158	P	V	T'	V	S	W	N	S	G	A	L	T	S	G	V	H	T	F	P	A
601	GTO	CCTA	CAC	GT	CCTC	AGGA	CT	CTAC	TCC	CTC	AGO	CAGO	CGT	3 G	TGAC	CGT	3CC	CTCC	CAGO	CAGC
150	CAC	≆GA′I	GT	CA	GGAG'	rcci	'GA	GATO	AGC									GAGG	TCC	STCG
T \ R	V	L	Q	S	S	\boldsymbol{G}	$oldsymbol{L}$	Y	S	L	S	S	V	V	T	V	P	S	S	S
										J.	28	3/	1							



Hsei et al.

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661 ITGGGCACCC AGACCTACAT CTGCAACGTG AATCACAAGC CCAGGAACAC CAAGGTGGAC GGTCGTTGTG GTTCCACCTG TTAGTGTTCG AACCCGTGGG TCTGGATGTA GACGTTGCAC

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(SEQ ID NO.44) (SEQ ID NO.43) 721 AAGAAAGTTG AGCCCAAATC TTGTGACAAA ACTCACACAT GA TTCTTTCAAC TCGGGTTTAG AACACTGTTT TGAGTGTGTA CT 218

-1G. 28B



Hsei et al.
Appl. No.: 09/234,182 Atty De Atty Docket: GENENT.093A

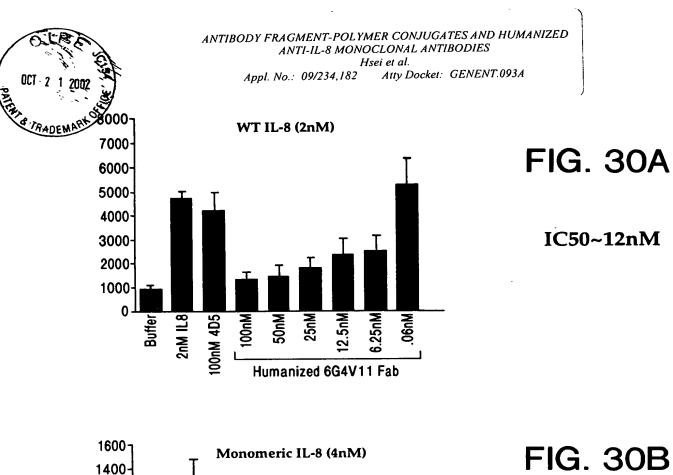
Variable Light Chain Domain

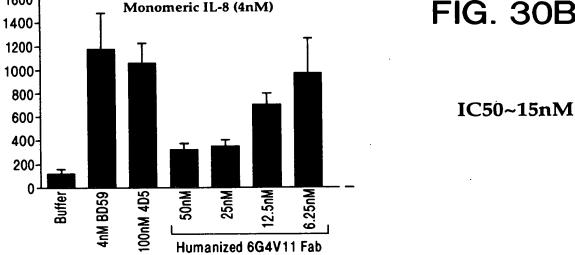
6G425	10 20 abcde 30 40 DIVMTQTPLSLPVSLGDQASISCRSSQSLVHGIGNTYLHWYLQKPGQSPKLLIY
F(ab)-1	# # # # # ## # ## # ## # ## DIQMTQSPSSLSASVGDRVTITCRSSQSLVHGIGNTYLHWYQQKPGKAPKLLIY # ###################################
humĸI	DIQMTQSPSSLSASVGDRVTITCRASKTISKYLAWYQQKPGKAPKLLIY

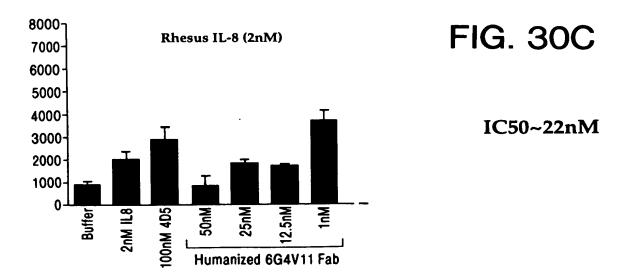
	L1
6G425	50 60 70 80 90 100 YKVSNRFSGVPDRFSDSGSGTDFTLRISRVEAEDLGLYFCSQSTHVPLTFGAGTKLELKR (SEQ ID NO.45)
	# # # # # # # # # # # # # # # # # # #
F(ab)-1	YKVSNRFSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCSQSTHVPLTFGQGTKVEIKR (SEQ ID NO.46)
	AR 888
humĸI	YSGSTLESGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQHNEYPLTFGQGTKVEIKR (SEQ ID NO.47)

	L2 L3
	Variable Heavy Chain Domain

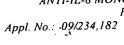
	10	20	30	40				
6G425	EIQLQQSGPELMKPG#	SVKISCKASG	YSFSSHYMH	WVKQSHO	KSLEWI			
		1 888 D.		# ##				
F(ab)-1	EVQLVESGGGLVQPGC	SLRLSCAASG	YSFSSHYMH	WVRQAPG	KGLEWV			
humIII	EVQLVESGGGLVQPGG	SLRLSCAASG	FSFTGHWMN	WVRQAPG	KGLEWV			
		=	=====					
		•	++++					
			H1					
	50 a	70	80	abc	90	100	110	
6G425	GYIDPSNGETTYNQK	KGKATLTVDT	SSSTANVHL	SSLTSDD	SAVYFCAAR	GDYRYNGDWI	FFDVWGAGT (SE	O ID NO.48)
			** ****					•
F(ab)-1	GYIDPSNGETTYNQK	KGRFTISRDN	SKNTLYLQM	NSLRAED	TAVYYCAAR	GDYRYNGDWI	FFDVWGQGT (SE	O ID NO.49)
							,	
humIII	GMIHPSDSETRYADSV	/KGRFTISRDN	SKNTLYLQM	NSLRAED	TAVYYCAAR	GIYFY-GTT	FDYWGQGT (SE	Q ID NO.50)
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	н2					Н3		







Atty Docket: GENENT.093A





Amino Acid Sequence of the humanized anti-IL-8 6G4.2.5V11 Light Chain

HVPLTFGOGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN **ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG** LHWYQQKPGKAPKLLIYKVSNRFSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCSQST MKKNIAFLLASMFVFSIATNAYADIQMTQSPSSLSASVGDRVTITCRSSQSLVHGIGNTY EC (SEQ ID NO.51) Amino Acid Sequence of the humanized anti-IL-8 6G4:2.5V11 Heavy Chain

WVRQAPGKGLEWVGYIDPSNGETTYNQKFKGRFTLSRDNSKNTAYLQMNSLRAEDTAVYY CARGDYRYNGDWFFDVWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYF PEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT@TYICNVNHKPSNTK MKKNIAFLLASMFVFSIATNAYAEVQLVQSGGGLVQPGGSLRLSCAASGYSFSSHYMH VDKKVEPKSCDKTHT (SEQ ID NO.52) Amimo Acid Sequence of the peptide linker and M13 Phage Coat (gene-IIII)

SGGGSGSGDFDYEKMANANKGAMTENADENALQSDAKGKLDSVATDYGAAIDGFIGDVS GLANGNGATGDFAGSSNSQMAQVGDGDNSPLMNNFRQYLPSLPQSVECRPFVFSAGKPY EFSIDCDKINLFRGVFAFLLYVATFMYVFSTFANILRNKES (SEQ ID NO.53)

FIG. 31A

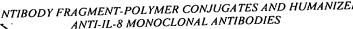
ANTIBODY FRAGMENT-POLYMER CONJUGATES AND HUMANIZED ANTI-IL-8 MONOCLONAL ANTIBODIES Hsei et al. Appl. No.: 09/234,182 Atty De

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				•																
EMARY	AT	GAA	AAA	GA	АТАТ	CGC	TTA	тст	TCT	TGCA	TC	TAT	GTI	CG	тттт	TTC	ТАТ	TGC	TAC.	AAAC
	TA	CTT	TTT	СТ	TATA	GCG'	ΓAΑ	AGA	AGA	ACGT	AG	ATA	CAA	.GC	AAAA	AAAG	ATA	ACG.	ATG	TTTG
-23	M	K	K	N	I	A	F	L	L	A	S	M	F	V	F	S	I	A	T	N
.:1 61	CC	አጥአ	ccc	m~	АТАТ	CCM	חמר	CAC	CC 3/	CMCC	CC	C N C	сmс		momo		CMC	mcm.	~~~	00 A M
01					TATA															
-3			A			Q			Q			s				A			G	
121					TCAC															
1.0		CCA(V		GT	AGTG	GAC(C				AGTT O		GAA L					TCC G			
10	K	V	•	_	•	C	K	3	3	Q	3	ים	V	п	G	_	G	N	Т	Y
181	TT	ACA	CTG	GT	ATCA	ACA	GAA	ACC.	AGG	AAAA	GC	TCC	GAA	AC	TACT	'GAT	ТТА	CAA	AGT	ATCC
					TAGT			TGG	TCC'	TTTT	CG.	AGG	CTT	TG	ATGA	CTA	ААТ	GTT	rca:	PAGG
38	L	Н	W	Y	Q	Q	K	P	G	K	A	P	K	L	L	I	Y	K	V	S
241	AA	TCG	ል ጥጥ _የ	СT	CTGG.	ልርጥ(יייר	ጥጥር።	ፐርር	רישישרי	יירי	тсс	ልጥ ር	CG	ርሞጥር	ካጉርር	CAC	CCA	יחיחיו	ጉልሮመ
					GACC															
58	N	R	F	S	G	V	P	S	R	F	S	G	s	G	S	G	${f T}$	D	F	T
204																				
301					GCAG CGTC															
78		T		S		L		P		D		acu A		Y	Y		AAG S	0	S	T T
				_	_	_	~	_	_		-		-	_	-	•	_	×	_	•
361					TCAC															
0.0					AGTG															
98	н	V	P	ь	т	F	G	Q	G	T	K	V	E	I	K	R	Т	V	A	Α
421	CC.	ATC'	TGT	СT	TCAT	СТТС	CCC	GCC	ATC'	TGAT	GA	GCA	GTT	GA	AATC	TGG.	AAC	TGCT	rrci	TTDT
	GG'	TAG	ACA	GΑ	AGTA	GAA	GGG	CGG'	TAG	ACTA	CT	CGT	CAA	CT	TTAG	ACC'	TTG	ACGA	\AG/	ACAA
118	P	S	V	F	I	F	P	P	S	D	E	Q	L	K	S	G	T	A	S	V
481	СТ	стс	CCጥ	GC.	TGAA	ጥ ልል(тфф	רים מיי	דיכיכים	CAGA	CA	200	ממר	λC	ጥልሮል	CTC	ממבי	ССТС	ייע בייב	רא א רי
401					ACTT															
138					N															
541					CGGG															
158					GCCC.												<i>3</i> ΤΤ Κ			T T
		_	•	_		- ,	_	×	_	J	•	•	~	×						•
601	TA	CAG	ССТ	CA	GCAG	CAC	CCT	GAC	GCT	GAGC	AA	AGC	AGA	СT	ACGA	GAA	ACA	CAAA	\GT(TAC .
470					CGTC															
178	Y	S	L	S	S	T	L	Т	Ь	S	K	Α	D	Y	E	K	Н	K	V	Y
661	GC	CTG	CGA	AG	TCAC	CCA	ГСА	GGG	CCT	GAGC	TC	GCC	CGT	CA	CAAA	GAG	CTT	CAAC	AGG	GGA
	CG	GAC	GCT'	TC	AGTG															
198	A	С	E	V	T	H	Q	G	L	S	S	Ė	V	T	K	S	F	N	R	G
721	CA	وبروي	ጥጥ አ	ΔG	CTGA	ייטיי	ירטיו	ACC	2000	2 0 00	CNI	ייטיי	rcc.	CC	CMAC	ጥ አ 🕶	א רויב	(SEQ	ID N	O.54)
					GACT															
218					ID NO							_		_	- ·- - ·	,				-

FIG. 31B



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Amino Acid Sequence of the humanized anti-IL-8 6G4.2.5V19 Light Chain

LHWYQQKPGKAPKLLIYKVSNRFSGVPSRFSGSGSGTDFTLTISSL@PEDFATYYCSQST HVPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLINNFYPREAKVQWKVDN **ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG** MKKNIAFLLASMFVFSIATNAYADIQMTQSPSSLSASVGDRVTITCRSSQSLVHGIGNTY EC (SEQ ID NO.51) Amino Acid Sequence of the humanized anti-IL-8 6G4.2.5V19 Heavy Chain

WVKQ**A**PGKGLEWVGYIDPSNGETTYNQKFKGRFT**L**SRDNSKNT**A**YLQMNSLRAEDTAVYY PEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTK CARGDYRYNGDWFFDVWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYF MKKNIAFLLASMFVFSIATNAYAEVQLVESGGGLVQPGGSLRLSCAASGYSFSSHYMH VDKKVEPKSCDKTHT (SEQ ID NO.55)

FIG. 31C

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ANTI-IL-8 MONOCLONAL ANTIBODIES

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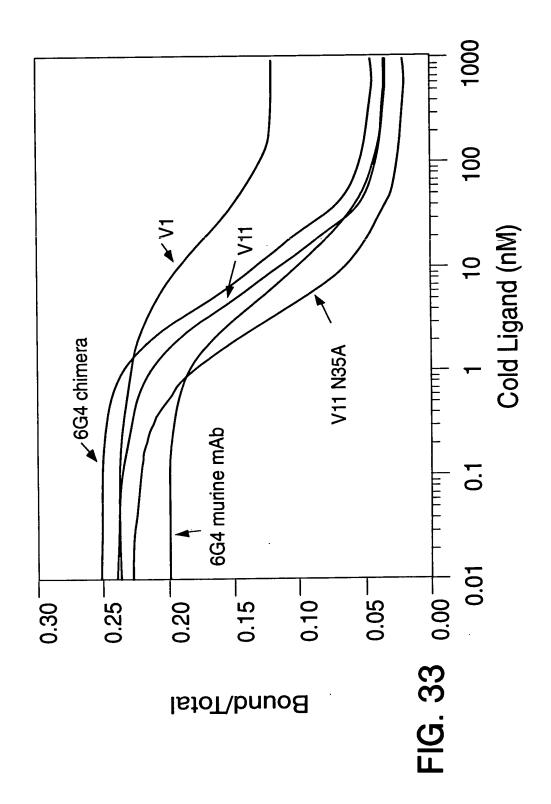
Appl. No.: 09/234,182 Atty Docket: GENENT.093A

FIG. 32

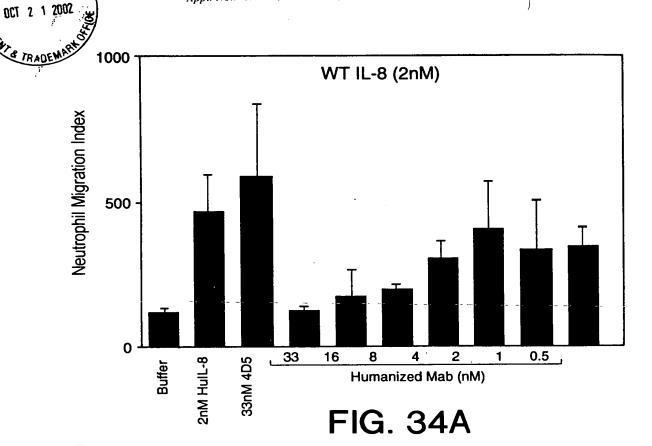




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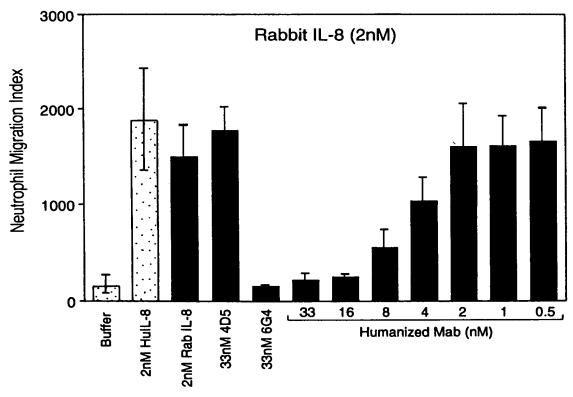
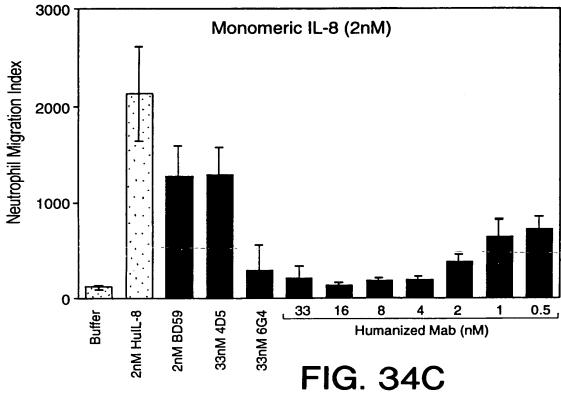


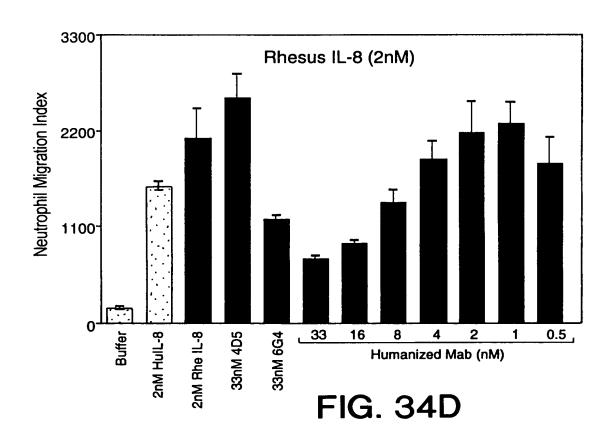
FIG. 34B



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Amino Acid Sequence of the humanized anti-IL-8 6G4.2.5V11N35A Light Chaim

ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG MKKNIAFLLASMFVFSIATNAYADIQMTQSPSSLSASVGDRVTITCRSSQSLVHGIGATY HVPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN LHWYQQKPGKAPKLLIYKVSNRFSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCSQST EC (SEQ ID NO.56) Amino Acid Sequence of the humanized anti-IL-8 6G4.2.5V11N35A Heavy Chain

CARGDYRYNGDWFFDVWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYF PEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTK **WVROAPGKGLEWVGYIDPSNGETTYNOKFKGRFTLSRDNSKNTAYLOMNSLRAEDTAVYY** MKKNIAFLLASMFVFSIATNAYAEVQLVQSGGGLVQPGGSLRLSCAASGYSFSSHYMH VDKKVEPKSCDKTHT (SEQ ID NO.52) Amimo Acid Sequence of the putative Pepsin Cleavage Site and GCN4 Leucine Zipper

CPPCPAPE<u>LL</u>GGRMKQLEDKVEELLSKNYHLENEVARLKKLVGER (SEQ ID NO.57)

FIG. 35

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EMARK	;					
1					TTTTTTCTAT AAAAAAGATA	
-23					F S I	
61					TGTCCGCCTC ACAGGCGGAG	
-3	A Y A D				\$ A S	
121					ATGGTATAGG TACCATATCC	
18					G I G	
181					TACTGATTTA ATGACTAAAT	
38					L I Y	
241					GTTCTGGGAC CAAGACCCTG	
58					S G T	
301					ATTACTGTTC TAATGACAAG	
78	L T I S				Y C S	
361					TCAAACGAAC AGTTTGCTTG	
98					K R T	
421					AATCTGGAAC TTAGACCTTG	
118				•	S G T	
481					TACAGTGGAA ATGTCACCTT	
138					Q W K	
541					AGGACAGCAA TCCTGTCGTT	
158	00000				D S K	
601					ACGAGAAACA TGCTCTTTGT	
178	Y S L S			K A D Y		K V Y
661					CAAAGAGCTT GTTTCTCGAA	
198	A C E V				K S F	N R G (SEQ ID NO.58)
721	GAGTGTTAAG	CTGATCCTCT	ACGCCGGACG	CATCGTGGCC	CTAGTACGCA	

FIG. 36

218 E C O (SEQ ID NO.56)

CTCACAATTC GACTAGGAGA TGCGGCCTGC GTAGCACCGG GATCATGCGT TGATCAGCAT

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DEMARK	र					
781	AAAAGGGTAT	CTAGAGGTTG GATCTCCAAC				
-1				M K K N	IAF	LLA
841		TTTTTTCTAT AAAAAAAGATA				
-11	S M F V		ATN	A Y A E		V Q S
901		TGGTGCAGCC ACCACGTCGG				
8		V Q P				
961		GTCACTATAT CAGTGATATA				
28		H Y M			G K G	
1021		TTGATCCTTC				
48		AACTAGGAAG D P S				
1081	TTCACTTTAT	CTCGCGACAA	CTCCAAAAAC	ACAGCATACC	TGCAGATGAA	CAGCCTGCGT
68	AAGTGAAATA F T L S	GAGCGCTGTT R D N	GAGGTTTTTG S K N	TGTCGTATGG T A Y L	ACGTCTACTT Q M N	GTCGGACGCA S L R
1141	GCTGAGGACA	CTGCCGTCTA	TTACTGTGCA	AGAGGGGATT	ATCGCTACAA	TGGTGACTGG
88		GACGGCAGAT	AATGACACGT	TCTCCCCTAA		ACCACTGACC
		TCTGGGGTCA				
	AAGAAGCTGC	AGACCCCAGT	TCCTTGGGAC	CAGTGGCAGA	GGAGCCGGAG	GTGGTTCCCG
	F F D V		G T L	V T V S	S A S	T K G
1261		TCCCCCTGGC AGGGGGACCG				
128	P S V F	PLA	P S S	K S T S	G G T	AAL
1321		TCAAGGACTA AGTTCCTGAT				
148	G C L V		F P E	P V T V		S G A
1381		GCGTGCACAC				
168		CGCACGTGTG V H T				
1441		TGACCGTGCC				
188	TCGTCGCACC	ACTGGCACGG T V P	GAGGTCGTCG S S S	AACCCGTGGG L G T Q	TCTGGATGTA T Y I	GACGTTGCAC C N V
1501		CCAGCAACAC				
208		GGTCGTTGTG S N T				
1561		GCCCGCCGTG				
228	TGAGTGTGTA T H T C	CGGGCGGCAC PPC	GGGTCGTGGT P A P	CTTGACGACC E L L G	CGCCGGCGTA G R M	CTTTGTCGAT K Q L

FIG. 37A



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1621 GAGGACAAGG TCGAAGAGCT ACTCTCCAAG AACTACCACC TAGAGAATGA AGTGGCAAGA CTCCTGTTCC AGCTTCTGA TGAGAGGTTC TTGATGGTGG ATCTCTTACT TCACCGTTCT 248 E D K V E E L L S K N Y H L E N E V A R

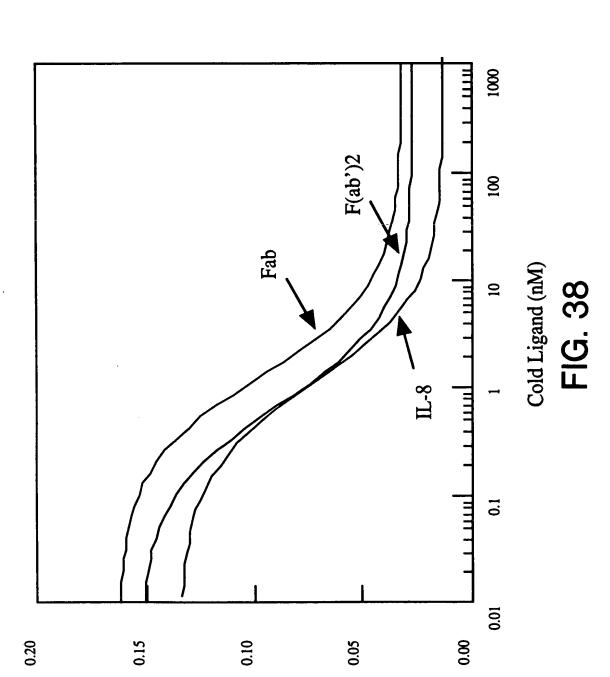
1681 CTCAAAAAGC TTGTCGGGGA GCGCTAA (SEQ ID NO.59)
GAGTTTTCG AACAGCCCCT CGCGATT

68 L K K L V G E R O (SEQ ID NO.60)

FIG. 37B



Appl. No.: 09/234,182 Atty Docket: GENENT.093A



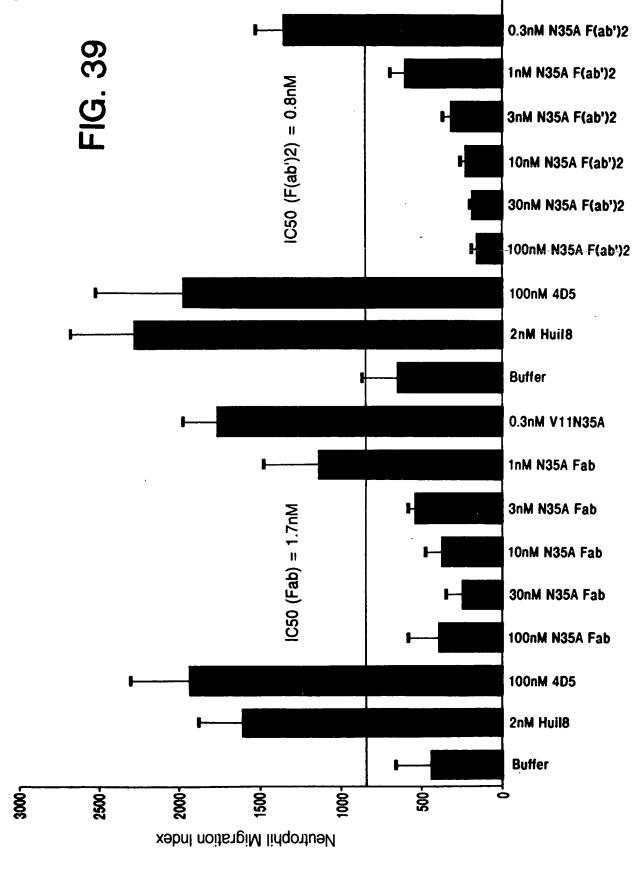
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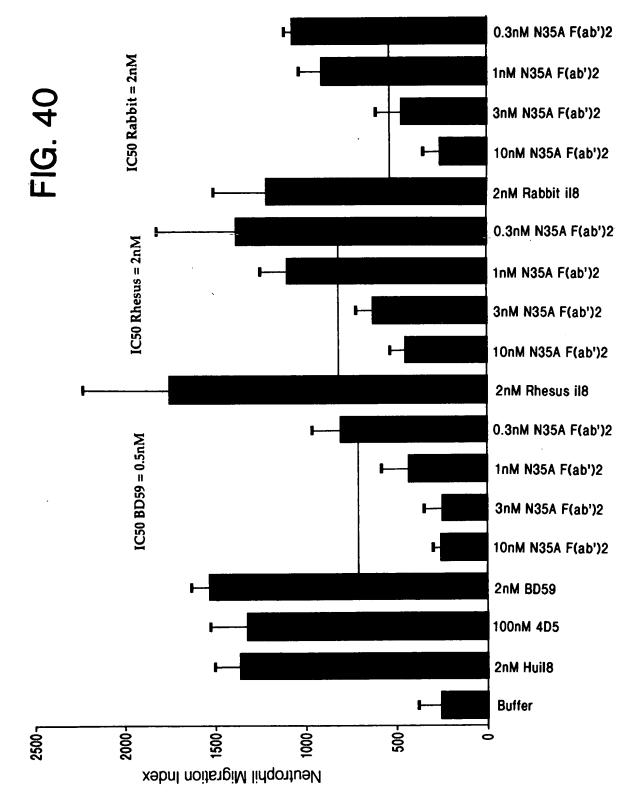
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mnlI

sfani

GGGCGCTGTA CGAGGTAAAG CCCGAIGCCA GCAITCCIGA CGACGAIACG GAGCIGCIGC GCGAITACGI AAAGAAGITA IIGAAGCAIC CICGICAGIA CCCGCGACAT GCTCCATTIC GGGCTACGGT CGTAAGGACT GCTGCTATGC CTCGACGACG CGCTAATGCA TETCTTCAAT AACTICGTAG GAGCAGTCAT

hinPI bsaAI

bbvI

hhaI/cfoI

aluI

DsmI

cac8I sfani

hhal/cfoI mnlI

haell csp6I

201



pleI

mbol/ndeII[dam-] GAATTCAACT ICTCCATACT ITGGATAAGG AAATACAGAC ATGAAAAATC ICATTGCTGA GITGTTATIT AAGCTTGCCC AAAAAGAAGA AGAGTCGAAT CTTAAGTIGA AGAGGIAIGA AACCIAITCC ITTAIGICIG IACTITITAG AGIAACGACT CAACAAIAAA ITCGAACGGG ITITICTICI ICICAGCITA 101 GAACTGTGTG CGCAGGTAGA AGCTTTGGAG ATTATCGTCA CTGCAATGCT TCGCAATATG GCGCAAAATG ACCAACAGCG GTTGATTGAT CAGGTAGAGG CTIGACACAC GCGICCAICI ICGAAACCIC IAAIAGCAGI GACGIIACGA AGCGIIAIAC CGCGIIIIAC IGGIIGICGC CAACIAACIA GICCAICICC bclI[dam-] mnlI earI/ksp632I mboli taqi dpnII[dam-] mbolI hinfl dpnI[dam+] sau3AI ISPBII hindIII msel cac8I tru9I snaBI hhaI/cfoI fouDII/mvoI **bsh1236I** hinPI fnu4HI bstUI thaI fou4HI bsoFI bbvi bsoFI bsrDI maeIII bsrDI nlaIII mslī avill/fspl hindill pflMI bslI hhai/cfoi **DSpMI** hinPI rsal hinPI ecoRI apoI

hgiAI/aspHI ecl136II **bsp1286 DSIRKAI** hgiJII aluI bmyI sstI sacI ecoRI mael rmaI eagI/xmaIII/eclXI haeIII/palI cfri BCLI eaeI

TITICAAITA GAAAAGITGI CGACAGIAIT ICAACAGIGC CGGCICIGAA IAICAGCGAA ACAAAAIAA AAAAITACAI AAACAITGAI CITAAGCICG

301 ABARCITAAT CITITCAACA GCTGTCATAA AGIIGICACG GCCGAGACII ATAGICGCII IGIITIAII IIITAAIGIA IIIGIAACIA GAAIICGAGC

bsmAI

maelll

nspBII

aluI DVuII

> tru9I nseI

ahdI/eam1105I

bsiEI

maelii apol banii

taqI

bfaI

tru9I mseI

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401 TCGGTACCCG GGGATCCTCI CGAGGTIGAG GIGAITITAI GAAAAAGAAI AICGCAITIC IICTIGCAIC TAIGTICGII ITTICIAITG CTACAAACGC AGCCATGGGC CCCTAGGAGA GCTCCAACTC CACTAAAATA CTTTTTCTTA TAGCGTAAAG AAGAACGTAG ATACAAGCAA AAAAGATAAC GATGTTTGCG The penultimate nucleotide was changed fr G toT ^ SIA M F V L A S sfani Iloqu a mutation was found that inactivated the mluI site. K K N alwi[dam-] mnli mnli mbol/ndeII[dam-] nlaIV paeR7I sau3AI taqI kpnI cauII dpnII[dam-] bamHI avaI bstYI/xhoII bani bsaJi alwi[dam-] dpnI[dam+] avaI csp6I asp718 acc65I hgici nlaIV rsaI

xhoI

cauli bsaJi

xmaI/pspAI

SCIFI

SmaI

ncil

hpall

dsaV

SCIFI

ncil

moli

nlaIII 501 ATACGCTGAT ATCCAGATGA CCCAGTCCCC GAGCTCCCTG TCGGCCTCTG TGGGCGATAG GGTCACCATC ACCTGCAGGT CAAGTCAAAG CTTAGTACAT hindIII csp6I rsaI ddeI aluI bspMI sse8387I pstI scfI bstEII hphI bsgI bspMI maeIII moli acil hgiAI/aspHI ec1136II **bsp1286 bsiHKAI** hgiJII bsrI aval aluI tth1111/aspI banII sacI DmyI bsmFI ecoRV

TATGCGACTA TAGGTCTACT GGGTCAGGGG CTCGAGGGAC AGGCGGAGAC ACCCGCTATC CCAGTGGTAG TGGACGTCCA GTTCAGTTTC GAATCATGTA Y A D I Q M T Q S P S S L S A S V G D R V T I T C R S S Q S L V H

FIG. 41B

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GAGCGAAGAG ACCTAGGCCA AGACCCTGCC TAAAGTGAGA CTGGTAGTCG TCAGACGTCG GTCTTCTGAA GCGTTGAATA ATGACAAGTG TCTCATGAGT

SIOP

ഗ

H

G T D

U

ဟ

<u>د</u> د bsaJI

csp6I

nlaIV

rsaI

styl

S

U

scal nlaIII TGGAICCGGI TCTGGGACGG ATTTCACTCT GACCAICAGC AGTCTGCAGC CAGAAGACTT CGCAACTIAT TACTGTICAC AGAGIACTCA 601 GGTATAGGTG CTACGTAITI ACACTGGTAI CAACAGAAAC CAGGAAAAGC TCCGAAACTA CTGAITTACA AAGTATCCAA TCGAITCTCI GGAGTCCCTT CCATAICCAC GAIGCAIAAA IGIGACCAIA GIIGICIIIIG GICCIIIICG AGGCIIIGAI GACIAAAIGI IICAIAGGII AGCIAAGAGA CCICAGGGAA csp6I rsaI hinfI bpmI/gsuI[dcm-] pleI **bsmFI** claI/bsp106 bspDI[dam-] tfiI bpuAI Ilodm ppsI fnu4HI **bsoFI** bbvI scfI pstI Ipsq aluI apyI[dcm+] v ecoRII bstNI dsaV mvaI × **DSMFI** mbol/ndeII[dam-] dpnII[dam-] alwI[dam-] bstYI/xhoII dpnI[dam+] alwI[dam-] hpail TYL Idsm bslI bsaWI sau3AI nlaIV bamHI 701 CICGCIICIC ы В

ACGITICGAC AGGGIACCAA GGIGGAGAIC AAACGAACIG IGGCIGCACC AICIGICIIC AICITCCCGC CAICIGAIGA GCAGIIGAAA CGTCAACTTT CCACCTCTAG TITGCTTGAC ACCGACGTGG TAGACGAAAG TAGAAGGGCG GTAGACTACT IIoqu bpuAI bbsI bsoFI bbvI RTV dpnII[dam-] dpnI[dam+] H TGCAAACCTG TCCCATGGTT asp718 acc651 maell 801 TGTCCCGCTC ACAGGGCGAG acil **bsmFI** 66

IIoqu

fnu4HI

mbol/ndell[dam-]

sau3AI

hgiCI

banI

berBI

kpnI

FIG. 41C

Atty Docket: GENENT.093A Appl. No.: 09/234,182

ecoRI1

dsaV

BCLFI

mvaI

maeIII apyI[dcm+] **b**stnI cac8I bfaI mael rmaI baaJI sau96I GGAGGTTAGC CCATTGAGGG 1001 AGGAGAGTGT CACAGAGCAG GACAGCAAGG ACAGCACCTA CAGCCTCAGC AGCACCTGA CGCTGAGCAA AGCAGACTAC GAGAAACACA AAGTCTACGC TOCTOTORCA GEGETOTOGIC CIGIOGIICO IGIOGIGGAI GIOGGAGIOG IOGIGGGAOT GOGACIOGIT IOGIOTGAIG CICITIGIGI IICAGAIGOG 901 TCTGGAACTG CTTCTGTTGT GTGCCTGCTG AATAACTTCT ATCCCAGAGA GGCCAAAGTA CAGTGGAAGG TGGATAACGC CCTCCAATCG GGTAACTCCC S hgaI ø mbol/ndeII[dam-] moli ball CACGGACGAC TTATTGAAGA TAGGGTCTCT CCGGTTTCAT GTCACCTTCC ACCTATTGCG aluI dpnI[dam+] Ø D z mpli sau3AI Ω blpI/bpul102I K cell1/espI X X hgaI ddeI csp6I rsal haeIII/palI T L T REAKV fpu4BI haeI bsoFI mnlI mall bbvI r S ddeI ۵, ល scfI H cac8I asp700 hgiAI/aspHI ß Xani ec1136II bsp1286 cac81 **bsinkAI** hgiJII aluI sau96I banII haeIII/palI sstI n u sacī bmyI asul ddel S AGACCTTGAC GAAGACAACA **^** maeIII asp700 GTA တ S 132

1101 CTGCGAAGTC ACCCATCAGG GCCTGAGCTC GCCCGTCACA AAGAGCTTCA ACAGGGGAGA GTGTTAAGCT GATCCTCTAC GCCGGACGCA TCGTGGCCCT

aluI

maeIII

ecc01091/drall

alwNI[dcm-]

maellI

TICTCGAAGT TGICCCCTCT CACAATICGA

CGGCCAGTGT

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ы U

GACGCITCAG IGGGIAGICC CGGACICGAG

haeIII/palI

aguI

hpaII sfaNI

alwI[dam-]

dpnII[dam-] mspI

tru9I

nseI

CTAGGAGATG CGCCTGCGT AGCACCGGGA

o (SEO ID NO.56)

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Atty Docket: GENENT.093A /234,182

alwNI[dcm-]

bsp1286

dsaV bstNI hgiJII

bstNI bsoFI

banII

ppvI

acil hael

apy1[dcm+] bsaJI bmyI
haelII/palI apy1[dcm+]

maeI bfaI

mluI csp6I mnlI

bsh1236I

bstuI

aluI

ddeI

afliii

rmaI

fnuDII/mvnI

thaI

aluI

fnu4HI bsoFI bbvI Z C

	Appl. N	lo.: 09/2
CSP6I SPEI XDAI MDII MDII MDII STANI 1201 AGTACGCAAC TAGTCGTAAA AAGGGTATCT AGAGGTIGAG GTGATTTTAT GAAAAGAAT ATCGCATTC TTCTTGCATC TATGTTCGTT TTTCTATTG TCATGCGTTG ATCAGCATTT TTCCCATAGA TCTCCAACTC CACTAAAATA CTTTTTCTTA TAGCGTAAAG AAGAACGTAG ATACAAGCAA AAAAGATAAC -23	scrFI mvaI ecoRII dsaV	?I [fnu4HI XII
xbal mnli mnli AAGGGTATCT AGAGGTTGAG GTGATTTTAT TTCCCATAGA TCTCCAACTC CACTAAAATA		scrFI mvaI ecoRII
csp61 spel 1 AGTACGCAAC TAGTCGTAAA TCATGCGTTG ATCAGCATTT 3		rsaI bsiWI/splI thaT
1201		

hphI

bfal maeI rmaI

speI

csp6I rsaI

rmaI maeI bfaI 1301 CTACAAACGC GTACGCTGAG GTTCAGCTAG TGCAGTCTGG CGGTGGCCTG GTGCAGCCAG GGGGCTCACT CCGTTTGTCC TGTGCAGCTT CTGGCTACTC GATGTTTGCG CATGCGACTC CAAGTCGATC ACGTCAGACC GCCACCGGAC CACGTCGGTC CACGTCGAA GACCGATGAG တ R L S G VOPG C C SCIFI a VOLV Y A E TNA

hpaII dsaV cauli bslI Idsm ncil

xmaI/pspAI SmaI

SCIFI ncil

caull dsaV

SCIFI mvaI

ecoRII

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TRADEMARK DE
MADEM

dsav

bsaJI

ARM		palī	draII
maell bsaal TACGTATAAT ATGCATATTA T Y N	cac81 mnli cac81 ddel drdi GCCTGCGTGC TGAGGACACT GCCGTCTATT CGGACGCACG ACTCCTGTGA CGGCAGATAA L R A E D T A V Y Y	sau961 haeIII/palI sau961 nlaIV hgiJII bsp1286 bsp120I bmyI	agui apai styl asui mnli bsaji haelil/pali ecool091/drali GGCCTCCA CCAAGGGCCC CCGGAGGT GGTTCCCGGG A S T K G P
snaBI hphI ATGGTGAAAC TACCACTTTG G E T	mnli ddei drdi C TGAGGACACT G ACTCCTGTGA		asu apa si si muli bali/pal rrc rcgccrcca c sac S A S I
bsli sau3AI mbol/ndell[dam-] dpnl[dam+] alvl[dam-] alvl[dam-] ATATT GATCCTTCCA TATAA CTAGGAAGGT I D P S N	cac81 cac81 do GCCTGCGTGC CGGACGCACG	maeIII stEII I mplI	ecorii bsaji dsav bseri bstni espji bsaji hphi bsmBi apyi[dcm+] bsmBi CCCTGGT CACCGTCTCC GGGACCA GTGGCAGAGG L V T V S
bs sau3A mbol/ndell[dpl[dpn[] dpn[[dam-] alwi[TGGATATAT GATCC ACCTATATAA CTAGG	CAGATGAACA GTCTACTTGT Q M N S	maeII bstEII scrFI mvaI	ecoRII bsaJI asuI dsaV bseRI apaI bstNI esp3I styI asuI bsaJI hphI bsmBI mnlI bsaJI rGGGTCAAG GAACCCTGGT CACCGTCTC TCGCCTCCA CCAAGGGCCC ACCCCACTTC CTTGGACCA GTGGCAGAGG AGCCGAGGT GGTTCCCGGG W G Q G T L V T V S S A S T K G P
pleI bstNI bs11 taqI bsaJI bs11 taqI avaII nlaIV sau96I mbol/r xhoI asuI haeIII/palI asuI dpnIII avaI maeIII bsrI ecool091/draII haeIII/palI CTTCTCGAGT CACTATATGC ACTGGGTCG CCAGGCC CCATTCCCG ACCTTACCA ACCTATATAA F S S H Y M H W V R Q A P G K G L E W V G I I	scfl pstl bspMI bspMI AGCATACCTG TCGTATGGAC		
aval bstNI bsaJI bstNI sau96I apyI[dcm+ nlaIV sau96I haeIII/palI asuI eco0109I/draII haeIII/palI AGGCCCCG GGTAAGGGCC TGGAAT TCCGGGGC CCATTCCCGG ACCTTA	I CCAAAAACAC GGTTTTTGTG K N T	·	maell hinll/acyl ahall/bsaHl taql mboll aatll T CTCGACGTC TGGG A GAAGCTGCAG ACCC
aval bsaJI sau96I nlaIV haeIII/palI asuI eco0109I/dra TCAGGCCCCG GGT	thaI fnuDII/mvnI bstUI bsh1236I nruI Tr CGCGACAACT SA GCGCTGTTGA		maeIII hphi bsri ml G GTGACTGGTT C CACTGACCAA G D W F
sau96I avaII asuI nlaIV bsrI ACTGGGTCCG	thal fnubli/mvni fnubli/mvni haelii/pali bstui bshl236i asuj nrul AGGCCGTT CACTTATCT CCCACAACT CCAAAAACAC TCCCGGCAAA GTGAAATAGA GCGCTGTTGA GGTTTTTGTG G R F T L S R D N S K N T		h CGCTACAATG GCGATGTTAC R Y N G
pleI hinfI sau96I taqI xhoI paeR7I avaI maeIII CTTCTCGAGT CACTATATGC ACTGGGTCCG GAAGAGCTCA GTGATATACG TGACCCAGGC F S S H Y M H W V R			maeIII hphl bsri mt ACTGTGCAAG AGGGATTAT CGCTACAATG GTGACTGGTT TGACACGTTC TCCCCTAATA GCGATGTTAC CACTGACCAA C A R G D Y R Y N G D W F
	L CAAAAGTTCA GTITTCAAGT 2 Q K F K		
1401	1501		1601

seq right is from p6G425chim2.fab2

Hsei et al.

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hphi mspi hpaii cfriol/bsrFi bsaWi tthiiii/aspi bsli agel maelii bsl agel maelii TACT TCCCCGAACC GGTGACGGTG ATGA AGGGCTTGG CCACTGCCAC	fnu4HI bsoFI maeIII mnli ddel hphi bsp1286 nli bbvi bstEli bmyl bpml/gsul[dcm-] cTCAG CAGCGTGGTG ACCGTGCCCT GAGTC GTCGCACCAC TGGCACGGGA L S S V V T V P S
SCIFI MUAI SCIFI MUAI SCIFI MUAI SCIFI MUAI SCORII SCORIII SCORII SCORII SCORIII SCORII SCORIII SCORII SCORIII SCORIIII SCORIII SCORIIII SCORIII SCORI	hinp! hal/cfol hal/cfol hal/cfol hal/cfol hal/cfol hal/cfol hal/cfol hal/cfol hal/sapl186 kas1 hinlI/acyl cac81 hinlI/acyl hall hall hall hall hall hall hall ha
nlaIV hgiCI banI scrFI mvaI ecoRII dsaV hgiAI/aspHI dsaV bpuAI apyI[dcm+] mnlI bsiHKAI bbsI bsaJI mnlI bmyI mnlI 1701 ATCGGTCTC CCCTGGCAC CTCCTCCAA GAGCACCTC TAGCCAGAAG GGGACCGTG GGGACCGTG GAGGAGGTT CTCGTGGAG	hinPI hhal/cfol hhal/cfol hal/cfol hal/

CCCGIGGGIC IGGAIGTAGA CGTIGCACTI AGIGTICGGG ICGTIGIGGT ICCAGCIGIT CTITICAACTC GGGTTAAGAA CACTGTITIG G I Q I Y I C N V N H K P S N I K V D K K V E P K S C D K I GGCCACCCAG ACCTACATCT GCAACGTGAA TCACAAGCCC AGCAACACCA AGGTCGACAA GAAAGTTGAG CCCAAATCTT GTGACAAAAC

bsp1286 hgiJII

banII bmyI

styl hincil/hindil

hinfi tfiI

hgiCI banI bsp1286 bmyI

fnu4BI bsofi bbvi 1901 CCAGCAGCTT GGTCGTCGAA S

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bstXI

maell

bsaJI accI

taqI salI

Hsei et al.

SCIFI

Appl. No.: 09/234,182

Atty Docket: GENENT.093A



bfaI rmaI mael 2001 TCACACATGC CCGCCGTGCC CAGCACCAGA ACTGCTGGGC GGCCGCATGA AACAGCTAGA GGACAAGGTC GAAGAGCTAC TCTCCAAGAA CTACCACCTA GATGGTGGAT AGIGIGIACG GCCGCCACGG GICGIGGICI IGACGACCCG CCGCCGIACI IIGICGAICI CCIGIICCAG CIICICGAIG AGAGGIICII K earl/ksp6321 E E L aluI **II**oqu sapi tth11111/aspI tagI Ω aluI mplI 1 1 E bfaI rmaI maeI nlaIII 'junction between antibody and leucine zipper acil acil fnu4HI bsoFI bsiEI eaeI cfrI notI A P E **bsp1286** P P C P nspHI acil bmyI cac8I nlaIII Igen

eag1/xmaIII/eclXI

mcrI

haeIII/palI

fnu4HI

bsoFI

GCCGCCGGC GTTTTTATT CICITACIIC ACCGIICIGA GIIIIICGAA CAGCCCCICG CGAIICGIAC GCIGCCGGGA ICICAGGGAI IGCGAGCCAA CGGCGGCCCG CAAAAAIAA hpaII cauli Idsm dsaV ncil fnu4HI acil **bsoFI** 2101 GAGAATGAAG TGGCAAGACT CAAAAAGCTT GTCGGGGAGC GCTAAGCATG CGACGCCCCT AGAGTCCCTA ACGCTCGGTT **DemFI** hinfI sau96I pleI haeIII/palI bfaI maeI . rmaI asuI o (SEQ ID NO.60) blpI/bpull02I ddeI nlaIII IHdsu eco47III cac8I cellI/espI Idsu hhaI/cfoI hinPI haeII V G E R hindIII hinfI pleI

FIG. 41H

GITAACICAT GITIGACAGC ITAICAICGA TAAGCIITAA IGCGGIAGII IAICACAGII AAAIIGCIAA CGCAGICAGG CACCGIGIAI GAAAICIAAC CAAITGAGIA CAAACTGICG AAIAGIAGCI AITCGAAAII ACGCCAICAA AIAGIGICAA IIIAACGAII GCGICAGICC GIGGCACAIA CIIIAGAIIG

bspDI[dam-] mseI acil

aluI

hpai nlaili hincii/hindii

2201

tru9I mseI hpaI

clal/bsp106 tru91

aluI taqi hindili

nlaIV hgiCI

> tru9I mseI

banI

ANTIBODY FRAGMENT-POLYMER CONJUGATES AND HUMANIZED ANTI-IL-8 MONOCLONAL ANTIBODIES Hsei et al. No.: 09/234,182 Atty Docket: GENENT.093A

Appl. No.: 09/234,182



<u>Jen</u>	ARY	OFFO S													fpu4BI	FI	haeIII/palI			
									TCCATT	AGGTAA				1	fon	bsoFI		eaeI	cfrI	CTTTGG G AAA CC
							ecoRV		AT ATCG	TA TAGO							acil	mcrI	bsiEI	106 ACC6
/palI							Ð	acil	CTTGCGGG	SAACGCCC						hgiAI/aspHI	bsp1286	bsiHKAI	H	GCACTGTC
haeIII/palI		SCIFI		H	hpall	dsav bsli	Cauli	asuI	GGGCCT	CCCGGA						hgi	psp	bsi)	bmyI	CTCGGA
	san96I	S	ncil	Ilum Idsm	csp6I hp			cfr101/bsrFL asuI	TAC TGCC	ATG ACGG						н	hhaI/cfoI	bslI	/fspI	ACC CGTT TGG GCAA
				rsal	O	Idsm	hpall	cfr10	ATGCCGG	TACGGCC						hinPI	hhaI	mstI bslI	aviII/fspI	TATGCGC
									CTIGGIT	GAACCAA										CAATTTC
									CAT AG	GTA TC									sfaNI	TTG ATC
							<u> </u>	scfI	CTGTAGG	GACATCC		foI					н		•	ATATGCG TATACGC
sfaNI	SCIFI	mvaI	ecoRII	dsaV	bstNI	IJ	hphI apyI[dcm+]	foki scfi	TGGATG	ACCTAC	hinPI	hhaI/cfoI	тшаІ	maeI	H	haeII	eco47III	aI	18:	AGCGCT
	ß	É	ě	ğ	ă	bsaJI	hphI ag	naelli	STC ACC	CAG TGG			E	ma	nhe	fnu4HI	bsoFI	bbvI bf	cac8I cac8I	rgc rgcr
					nlaIV	mnll hqiCI	, H	banı	CGGCACC	GCCGTGG									Cac	TATGGCG
						mnlI	bsaJI	hhai/cfoi foki bani maelil	CATCCT	AGTAGGA								maeIII	BrI	CAGTCAC
								foI	A TCG1	r AGC									sfaNI bsrI	7 CGC(
							hinPI	hhaI/C	2301 AATGCGCTCA TCGTCATCCT CGGCACCGTC ACCCTGGATG CTGTAGGCAT AGGCTTGGTT ATGCCGGTAC TGCCGGGCCT CTTGCGGGAT ATCGTCCATT	TTACGCGAGT AGCAGTAGGA GCCGTGGCAG TGGGACCTAC GACATCCGTA TCCGAACCAA TACGGCCATG ACGGCCCGGA GAACGCCCTA TAGCAGGTAA									sfa	2401 CCGACAGCAT CGCCAGTCAC TATGGCGTGC TGCTAGCGCT ATATGCGTTG ATGCAATTTC TATGCGCACC CGTTCTCGGA GCACTGTCCG ACCGCTTTGG GGCTGTCGTA GCGGTCAGTG ATACCGCACG ACGATCGCGA TATACGCAAC TACGTTAAAG ATACGCGTGG GCAAGAGCCT CGTGACAGGC TGGCGAAACC
									2301											2401

hpall sfaNI hgaI Idsm mbol/ndeII[dam-] dphII[dam-] bstYI/xhoII alwI[dam-] dpnI[dam+] alwI[dam-] moli sau3AI nlaIV bamHI mbol/ndeII[dam-] dpnII[dam-] dpnI[dam+] bstUI nlaIII fnuDII/mvnI sau3AI **bsh1236I** nlaIV

FIG. 41

GCCGCCCCCCT CAGGACGAGC GAAGCGATGA ACCTCGGTGA TAGCTGATGC GCTAGTACCG CTGGTGGGG CAGGACACCT AGGAGATGCG GCCTGCGTAG

CCCCCCCCA GICCIGCICG CIICGCIACI IGGAGCCACI AICGACIACG CGAICAIGGC GACCACACC GICCIGIGGA ICCICIACGC CGGACGCAIC

taqI

cac8I

acil bsrI

2501

fnu4HI acil

bsoFI

bslI

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fnu4HI

hhal/cfol hinPI

hpall

SCLFI

ncil Idsm nlaIV

narI kası

haeIII/palI

sau96I nlaIV

cauli

bslI dsaI

dsaV



hgiJII	bsp1286	bmyI	banII	sau3AI cac8I rcal hinPI	mbol/ndell[dam-] hgiJII haeII	dpn1[dam+] bsp1286 eco47III		mboil[dam-] banil nlaili	2601 GIGGCCGGCA TCACCGGCGC CACAGGIGCG GIIGCIGGCG CCIAIAICGC CGACAICACC GAIGGGGAAG AICGGGCICG CCACTICGGG CICAIGAGCG	LACCGGCCGT AGTGGCCGCG GTGTCCACGC CAACGACCGC GGATATAGCG GCTGTAGTGG CTACCCCTTC TAGCCCGAGC GGTGAAGCCC GAGTACTCGC	
				88	a	dp	dp	Ilodm Idqd	CGACATCACC GATGGGGAAG	GCTGTAGTGG CTACCCCTTC	
nlaIV	narI	kasI	hinlI/acyI	hgiCI	haeII	banI	ahaII/bsaHI	cac8I	GTTGCTGGCG CCTATATCGC	CAACGACCGC GGATATAGCG	
hinlI/acyI	hgici	haeII	Igem	cfr101/bsrFI banI	cac8I sgrAI	haeIII/pall hpaII	hphI ahaII/bsaHI	cfrl sfaNI cfrl01/bsrFI acil	TCACCGGCGC CACAGGTGCG	AGTGGCCGCG GTGTCCACGC	
	Idsm	hpaII	naeI	cfr101/	cac8I	haeIII/p	eaeI	cfrI sfa	2601 GTGGCCGGCA	CACCGGCCGT	

hhaI/cfoI

hinPI

hhaI/cfoI

nlaIV narI kası

hinPI

bsoFI hgiAI/aspHI acil bsp1286 fnu4HI bsiHKAI bsoFI bmyI	bsli acii acii haeIII/pali ACCATTCCTT GCGCGCGG TGCTCAACGG TGGTAAGGAA CGCCGCCGC ACGAGTTGCC
ninli/acyi ngiCi naeli nani	hall/bsaHl cac81 GGGCCATCT CCTTGCACGC CGGGGTAGA GGAACGTGCG
I Lu	bsmFI ahaI CGG GGGACTGTTG GGCG GCC CCCTGACAAC CCGC
nlaIV eael haeIII/palI asuI bsaJI bsaJI eco01091/draII	cac81 bs11 cfr1 bsmF1 aha11/bsaH1 cac81 bs11 aci1 aci1 hae 2701 CTTGTTTCG CGTGGGTATG GTGGCAGGC CCGTGGCCG GGGACTGTTG GGGGGGGG TGCTCAACGG GAACAAAGCC GCACCCATAC CACCGTCGG GGCACCGGCC CCCTGACAAC CCGCGGTAGG GGAACGTGCG TGGTAAGGAA CGCCGCCGCC ACGAGTTGCC

2801 CCTCAACCTA CTACTGGGCT GCTTCCTAAT GCAGGAGTCG CATAAGGGAG AGCGTCGTCC GATGCCCTTG AGAGCCTTCA ACCCAGTCAG CTCCTTCCGG GGAGTIGGAT GAIGACCCGA CGAAGGAITA CGICCICAGC GIAITCCCIC ICGCAGCAGG CIACGGGAAC ICICGGAAGI IGGGICAGIC GAGGAAGGCC

mspi hpaii bsaWi

bsrI aluI bslI

sfaNI

hgaI

hinfI

ecoNI bslI

fnu4HI bsoFI

bsrI bbvI

mall ball

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Atty Docket: GENENT.093A



moli 2901 resectedes scatsactat cstesectea cttatsacts tettettat catscaacte stassaces tsecssease setetsset attitesses ban! hpal! hhal/cfol cac8I eco47III mspI hinPI cfr101/bsrFI nael haell fnu4HI **DSOFI** bbvI nlaIV hgiCI nlaIII IIoqu bpuAI bbsI fpu4HI bsoFI acil nlaIII bcgI fnuDII/mvnI bsh1236I hhaI/cfoI bstuI acil hinPI thaI

ACCCGCGCCC CGTACTGATA GCAGCGGCGT GAATACTGAC AGAAGAAATA GTACGTTGAG CATCCTGTCC ACGCCCGTCG CGAGACCCAG TAAAAGCCGC

thaI

TCGCTGGAGC GCGACGATGA TCGGCCTGTC GCTTGCGGTA TTCGGAATCT TGCACGCCCT CGCTCAAGCC TTCGTCACTG GTCCCGCCAC TCCTGGCGAA AGCGACCTCG CGCTGCTACT AGCCGGACAG CGAACGCCAT AAGCCTTAGA ACGTGCGGGA GCGAGTTCGG AAGCAGTGAC CAGGGCGGTG acil DSMFI sau96I avall nlaIV asuI bsrI maelli cac8I mnlI hinfI acil cac8I haeIII/palI mbol/ndeII[dam-] bpmI/gsuI[dcm-] dpnII[dam-] dpnI[dam+] sau3AI fauDII/mvaI bsh1236I hhaI/cfoI bstuI hinPI AGGACCGCTT acil sau96I avall asuI 3001

bsh1236I foki haeIII/palI thal fnuDII/mvnI bsh1236I mnlI fpuDII/mvbI bstur bstur thaI hgaI nruI cacel maeII fnuDII/mvnI eagI/xmaIII/eclXI hhaI/cfoI **bsh1236I** hinPI bgli nlaili haelii/pali bstui thaI acil hgal fnu4HI bsiEI eaeI bsoFI cfrI MCLI cfr101/bsrFI haeIII/pall hpaII cac8I Idsm cac8I

FIG. 41K

GTTTGCAAAG CCGCTCTTCG TCCGGTAATA GCGCCCGTAC CGCCGGCTGC GCGACCCGAT GCAGAACGAC CGCAAGCGCT GCGCTCCGAC CTACCGGAAG

3101 CAAACGTTTC GGCGAGAAGC AGGCCATTAT

psp1406I

CECCGGCATG GCGCCGACG CGCTGGGCTA CGTCTTGCTG GCGTTCGCGA CGCGAGGCTG GATGGCCTTC

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Atty Docket: GENENT.093A

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alwI[dam-] 3201 CCCATTATGA ITCTTCTCCC ITCCGGCGGC ATCGGGATGC CCGCGTTGCA GGCCATGCTG ICCAGGCAGG IAGATGACGA CCATCAGGGA CAGCTTCAAG GGGTAATACT AAGAAGAGG AAGGCCGCCG TAGCCCTACG GGCGCAACGT CCGCTACGAC AGGTCCGTCC ATCTACTGCT GGTAGTCCCT GTCGAAGTTC bsmFI aluI apyI[dcm+] pspMI ecoRII SCIFI sfaNI bshl236I haeIII/pall bstNI dsaV mvaI cac8I nlaIII haeI fauDII/mvnI bstul acil cac8I sau96I fokI hpall sfaNI mslI fpu4BI **bsoFI** acil Idsm IIoqu fau4BI hinfI **bsoFI** acil thaI

GATCGCTCGC GGCTCTTACC AGCCTAACTT CGATCACTGG ACCGCTGATC GTCACGGCGA TTTATGCCGC CTCGGCGAGC ACATGGAACG GGTTGGCATG CTAGCGAGCG CCGAGAATGG TCGGATTGAA GCTAGTGACC TGGCGACTAG CAGTGCCGCT AAATACGGCG GAGCCGCTCG TGTACCTTGC CCAACCGTAC nlaIII hgiAI/aspHI bsp1286 **DSIHKAI** bmyI cac8I bsaJI mplI fpu4HI acil **bsoFI** bglI mbol/ndell[dam-] maeIII acil dpnII[dam-] dpnI[dam+] sau3AI dpn1[dam+] nspBII mbol/ndeII[dam-] sau3AI asuI dpnII[dam-] bsrI taqI[dam-] fnu4HI mbol/ndeII[dam-] sau3AI bsh1236I bstul dpnII[dam-] dpnI[dam+] cac8I

bsoFI

3301

hinPI

avall

fnuDII/mvnI

3401 GATTGTAGGC GCCGCCCTAT ACCTTGTCTG CCTCCCGGG TTGCGTCGCG GTGCATGGAG CCGGGCCACC TCGACCTGAA TGGAAGCCGG CGGCACCTCG hpaII nlaIV hgiCI cfr101/bsrFI banI fpu4HI **DSOFI** acil Idsm cac8I naeI taqI haeIII/palI moli sau96I nlaIV asuI hpaII nlalli cauli SCLFI ncil Idsm dsaV fnuDII/mvnI bsh1236I bsh1236I hgaI aciI bstul fnuDII/mvnI bstuI mnlI aciI ahaII/bsaHI hhaI/cfoI hinl1/acy1 banI acil nlaIV hqici haeII narI kasī

FIG. 41L

CTAACATCCG CGCGGGATA TGGAACAGAC GGAGGGGCGC AACGCAGCGC CACGTACCTC GGCCCGGTGG AGCTGGACTT ACCTTCGGCC GCCGTGGAGC

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cac8I

rmaI

mael

dsaV

sau96I

mbol/ndeII[dam-]

sau3AI

nlaIV avall asuI **DPuMI**

ncil

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fnuDII/mvnI thal acil hqaI pflMI hhaI/cfoI hinPI mstI

bsaJI bsli aviII/fspI

nlaIV

bsli

hinfI tfiI

pflMI

hphI

TCCCGTCCCC **bsh1236I** bstuI ·bsmI

GATIGCCIAA GIGGIGAGGI ICTIAACCIC GGIIAGIIAA GAACGCCICI IGACACIIAC GCGITIGGII GGGAACCGIC IIGIAIAGGI AGCGCAGGCG 3501 CTAACGGATT CACCACTCCA AGAATTGGAG CCAATCAATT CTTGCGGAGA ACTGTGAATG CGCAAACCAA CCCTTGGCAG AACATATCCA acil

haeIII/palI mscI/balI haeI

mval dsal SCIFI

Idsm

hpaII SCIFI

ecoRII dsaV

bslI bsaJI bstNI

apyI[dcm+] I96nes

hinPI avall

bsoFI fnuDII/mvnI

bstul

fpu4HI

fnu4HI bsoFI

thaI hinPI fnu4BI

dpnII[dam-]

dpnI[dam+]

hhal/cfol hgiAl/aspHI mstI nlaIII bsp1286 asuI eaeI

nlaIV cfrI IMndd fpu4BI

bsoFI bbvI bbvI acil bsh1236I avaI bsoFI cac8I hhal/cfoI

3601 CATCTCCAGC AGCCGCACGC GCCGCATCTC GGGCAGCGTT bpmI/gsuI[dcm-] acil sfaNI

GGGTCCTGGC CACGGGTGCG CATGATCGTG CTCCTGTCGT TGAGGACCCG GCTAGGCTGG

aviII/fspI bsiHKAI

DmyI

eco01091/drall msll

acil

mnll cauli-bfal

eco01091/draII

GTAGAGGTCG TCGGCGTGCG CCGCGTAGAG CCCGTCGCAA CCCAGGACCG GTGCCCACGC GTACTAGCAC GAGGACAGCA ACTCCTGGGC CGATCCGACC

fpu4HI fauDII/mval cac8I thaI

fnu4HI **bsoFI**

bbvI

bsh1236I maeII bstul hphī

maell

bsoFI bbvI

hinfI tfiI

bsrI

GCCCCAACGG AAIGACCAAI CGICTÍACTI AGIGGCTAIG CGCTCGCTIG CACITCGCIG ACGACGACGI ITIGCAGACG CIGGACICGI IGIIGIACIT 3701 CGGGGTTGCC TTACTGGTTA GCAGAATGAA TCACCGATAC GCGAGCGAAC GTGAAGCGAC TGCTGCTGCA AAACGTCTGC GACCTGAGCA ACAACATGAA

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	ည	LI FGA AGT	bslI 3cc 3cc
	HI 1 cac8I GCTGGCTACC CGACCGATGG	mnli TTTACCCTC	apoi b AGAAATTCCC TCTTTAAGGG
dam-]	fnu4 bsoF bbvI sfaNI fokI GCAGGATGCT	bsrI acil ccGccAGTTG TTTACCCTCA GGCGGTCAC AATGGGAGT	mnli foki maeIII sfaNI TCAGTAACCC GTATCGTGAG CATCCTCTT CGTTTCATCG GTATCATTAC CCCCATGAACA AGTCATTGG CATAGCACTC GTAGGAGAAG GCAAAGTAGC CATAGTAATG GGGGTACTTG
<pre>sau3AI mboI/ndeII[dam-] mamI[dam-] dpnI[dam+] dpnI[dam-] bstYI/xhoII alwI[dam-]</pre>	mspl hpall mrol bsaBl[dam-] bspMll bspEl[dam-] accll[dam-] TCCG GATCTGCATC AGGC CTAGACGTAG	acil boki sau96i sfaNi sau96i sfaNi nlaIV acil avall fnu4HI asul bsoFl TGATTTTCT CTGGTCCGC CGCATCCATA	GTATCATTAC CATAGTAATG
bs a1	mspi hpali mroi bi bspMii bspEi[bsaWi accili TTATGTTCCG G	acir bsmFi sau96i s nlaIV acii avaii fnu4H asui bsoFi CTGGTCCCGC CG	CGTTTCATCG
	hinPI hhal/cfoI aeII mslI GCG CCCTGCACCA		mnli foki maeili sfani rCAGTAACCC GTATCGTGAG CATCCTCT AGTCATTGG CATAGCACTC GTAGGAGAA
	acil thai fnuDil/mvni hinPi bstui hhai/ bsh1236i haeli CGCG GAAGTCAGCG C	dde.I TGACCCTGAG ACTGGGACTC	s: GTATCGTGAG CATAGCACTC
	acil thai fnuDil/m bstUi bsh1236I rGGAAACGCG GAA	cac8I hinPI hinPI hhal/cfoI tru9I haeII mseI eco47III TATTAACGAA GCGCTGGCAT	maeIII TCAGTAACCC AGTCATTGGG
	TCGTAAAGTC AGCATTTCAG	cac8I hinPI hinPI hhal/cfoI tru9I haeII mseI eco47III ddeI CCTACATCTG TATTAACGAA GCGCTGGCAT TGACCCTGG	nspl scrfl ncil mspl hpall dsaV nlalll caull maelll nspHl GTAACCGGC ATGTTCATCA
	mboli bpual bbsi rggrctrcg ttrccgrgtt rcgtaaagtc		
	mbolI bpuAI bbsI rggtctTCGG	3901 CTGTGGAACA GACACCTTGT	bsri bsli maeli psp14061 1 CAACGTTCCA (GTTGCAAGGT)
	3801	3901	4001

FIG. 41N



E

ANTIBODY FRAGMENT-POLYMER CONJUGATES AND HUMANIZED ANTI-IL-8 MONOCLONAL ANTIBODIES Hsei et al.

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tru9I msel bpmI/gsuI[dcm-] TATCAGAAGC CAGACATTAA CGCTTCTGGA GAAACTCAAC ATAGTCTTCG GTCTGTAATT GCGAAGACCT CTTTGAGTTG	fnu4HI thal bsoFI fnuDII/mvnI uI bstUI iii hinPI iii thal iii fnuDII/mvnI ii fnuDII/mvnI cancacacacacacacacacacacacacacacacacaca	hgal thal fnuDII/mvnI bstUI aciI bsh1236I hinPI nspBII hhal/cfoI actI ccccTCAG GGCGCTCAG CGCGTCAG
cac8I sau96I tru9I haeIII/palI mnlI maeIII acil nlaIII acil msel bpmI/gsul[dcm-] CCTTACACGG AGGCATCAAG TGACCAAAAAACC GCCCTTAACA TGCCCGCTT TATCAGAAGC CAGACATTAA CGCTTCTGGA GAAACTCAACGGGAATGTCC TCCGTAGTTC CCTTTTTTGG CGGGAATGTT ACCGGGCGAA ATAGTCTTCG GTCTGTAATT GCGAAGACCT CTTTGAGTTG	fnu4HI thaI bsoFI fnuDII/mvnI acil	bsmBI bsmAI psmAI mspI psoFI scrFI bbvI nciI psoFI scauli dsav mnlI nspHI alul bslI maeIII acii cauli drdI 4301 AAAACCTCTG ACACATGCAG CGGTCACAGC TTGTCTGTAA GCGGATGCC GGAGCAGACA TTGTGGAGAC CCTCGTGTT TCGGCCTCTT TCGGCCTCTT TCGCCTCTT TCGCCTCTT TCGCCTCTTT TCGCCCTCTTT TCGCCCTCTTT TCGCCCTCTTT TCGCCCTCTTT TCGCCTCTTT TCGCCTCTTT TCGCCTCTTT TCGCCTCTTT TCGCCTCTTT TCGCCTCTTT TCGCCTTTT TCGCTTTT TCGCCTTTT TCGCCTTTT TCGCTTTT TCGCTTTTT TCGCTTTT TCGCTTTT TCGCTTTT TCGCTTTT TCGCTTTT TCGCTTTT TCGCTTTTT TCGCTTTT TCGCTTTT TCGCTTTT TCGCTTTTT TCGCTTTT TCGCTTTT TCGCTTTT
cac81 sau961 sau961 tru91 haeIII/pal maeIII asuI 4101 CCTTACACG AGGCATCAAG TGACCAAACA GGAAAAAACC GCCCTTAACA TGGCCCCCTT GGAATGTGCC TCCGTAGTTC ACTGGTTTGT CCTTTTTTGG CGGGAATTGT ACCGGGCGAA	acil thai fnuDil/mvni xmni bstui tfii bshl236i hinfi al foki asp700 CG CGGAGACATC TGTGAATCGC TGGCC TGCCC CGCTCCTGTAGCC ACCTCTGTAGCC ACCTTCTAGCC ACCTTAGCC A	esp3i bsmBi bsmBi bsmAi mspi mspi nlali dsav nspi cauli nspli alul bsli maelli ACACATGCAG CTCCCGGAGA CGGTCACAGC TGTGTACGTC GAGGGCCTCT TGTGTACGTC GAGGGCCTTT TGTGTACGTC GACGACCATT
mbli 4101 CCTTACACGG AGG GGAATGTGCC TCC	acil thai fnuDII/mvnI bstUI bsh12361 aluI hgaI fokI 4201 GAGCTGGACG CGGATGAACA CTCGACCTGC GCCTACTTGT	mbli 4301 AAAACTCTG A TTTTGGAGAC T

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	という思いません	fnu4HI bsoFI bbvI hinPI nlaIII bsrI hhal/cfoI tth1111/	i ag pa	maeII neIII bsaAI aspI	acil ac	bst11071 tacci bsrI n	tru9I	sfaNI fnu4HI bsoFI acil	I P	ddel rsal csp61	hgiAl/asphir bsp1286 bsiHKAI bmyl ndel apaLI/snoI alw441/snoI
1044	GCCCACAGCC	CCGCGTCGGT	COCCACAGCC CCGCGTCGGT ACCATCGCTA TCGCCTCACA TATGATACGCC GTAGTCTCGT CTAACATGAC TCTCACGTGG mboli earl/ksp6321	TGCATCGCTA	TCGCCTCACA	TATGACCGAA mboli	CCGAA TTGATA(mboll	2 5 2 5 2 5 2 5 2 5 2 5 2 5 2 5 2 5 2 5	AGTCTCGT (CTAACATGAC	TCTCACGTGG
	T : C «		They		sfaNI	sapi hinPi hhal/cfoi	for acit molf	<u> </u>	plei	Ð	ifoI mcrI baiEI
4501	ATATGCGGTG	TGAAATACCG ACTITATGGC	CACA	TAAGGAGAAA ATTCCTCTTT	ATACCGCATC TATGGCGTAG	AGGCGCTCT TCCGCGAGA	FT CCGCTTC	SGAG CC	TCACTGAC	TCGCTGCGCT	CGGTCGTTCG
	fnu4HI bsoFI aciI fnu4HI	aciI							nlaIII nspI	III	bslI cac8I
4601	bsofi bsr bbvi cac81 GCTGCGGCCA CGACGCCGCT	bsofi bsrBi bbvi cac8i scrgcggcga gcgcrarcag crcacrcaaa cgacgccgcr cgccaragrc gagrgagtrr	bsofi bsrBi alui acii haelil/pa bbvi cac8i afilii hael 4601 GCTGCGGCGA GCGCTATCAAA GCCGCTATAT CCGTTATCCA CAGAATCAGG GGATAACGCA GGAAAGAACA TGTGAGCAAA AGGCCAGCAA CGACGCCGCT CGCCATAGTT CCGCCATTAT GCCAATAGGT GTCTTAGTCC CCTATTGCGT CCTTTCTTGT ACACTCGTTT TCCGGTCGTT	acil GGCGGTAATA CGGTTATCCA CCGCCATTAT GCCAATAGGT	CGGTTATCCA GCCAATAGGT	tfii hinfi CAGAATCAGG GTCTTAGTCC	SG GGATAA(SC CCTATT	CGCA GC	nspHI aflIII AAAGAACA TG	nspHI haeIII/pa afliII haeI GGATAACGCA GGAAAGACA TGTGAGCAAA AGGCCAGCAA CCTATTGCGT CCTTTCTTGT ACACTCGTTT TCCGGTCGTT	haeIII/palI haeI AGGCCAGCAA TCCGGTCGTT
	SCLFI	thaI	aI fnuDII/mvnI	IvaI							

4701 AAGGCCAGGA ACCGTAAAAA GGCCGCGTTG CTGGCGTTTT TCCATAGGCT CCGCCCCCCT GACGAGCATC ACAAAAATCG ACGCTCAAGT CAGAGGTGGC TTCCGGTCT TGGCATTTTT CCGGCGCAAC GACCGCAAAA AGGTATCCGA GGCGGGGGGA CTGCTCGTAG TGTTTTTAGC TGCGAGTTCA GTCTCCACCG

mplI

drdI tagI

sfaNI

acil

cac8I

bstUI bsh1236I

ecoRII dsaV bstNI

bslI

apyI[dcm+] haeIII/palI hael nlaIV

haeIII/palI fnu4HI bsoFI acil

plaIV

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alwNI[dcm-]

fnu4HI

Idsm

fou4HI

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hgiAI/aspHI

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4801 GAAACCCGAC AGGACTATAA AGATACCAGG CGTTTCCCCC TGGAAGCTCC CTCGTGCGCT CTCCTGTTCC GACCCTGCCG CTTACCGGAT ACCTGTCCGC CTTTGGCCTG TCCTGATATT TCTATGGTCC GCAAAGGGGG ACCTTCGAGG GAGCACGCGA GAGGACAAGG CTGGGACGGC GAATGGCCTA TGGACAGGCG hpall bsaWI fnu4HI Idsm **bsoFI** aciI bslIaluI mplI hhaI/cfoI bssSI apyI[dcm+] bsaJI bstNI dsaV apyI[dcm+] ecoRII bstNI dsaV

ecoRII

SCLFI

mvaI

SCLFI

mvaI

alw44I/snoI apaLI/snoI 4901 CTITCICCCI ICGGAAGCG IGGCGCITIC ICAIAGCICA CGCIGIAGGI AICICAGIIC GGIGIAGGIC GIICGCICCA AGCIGGGCIG IGIGCACGAA GAAAGAGGGA AGCCCTTCGC ACCGCGAAAG AGTATCGAGT GCGACATCCA TAGAGTCAAG CCACATCCAG GAAGCGAGGT TCGACCCGAC ACACGTGCTT bsp1286 **bsinkai** bmyI ddeI scfI aluI hhaI/cfoI hinPI haeII

maellI 5001 CCCCCCTTC AGCCCGACCG CTGCGCCTTA TCCGGTAACT ATCGTCTTGA GTCCAACCCG GTAAGACACG ACTTATCGCC ACTGGCAGCA GCCACTGGTA GGGGGCCAAG TCGGGCTGGC GACGCGGAAT AGGCCATTGA TAGCAGAACT CAGGTTGGGC CATTCTGTGC TGAATAGCGG TGACCGTCGT CGGTGACCAT bsrI **bsoFI** pbvI fnu4BI **bsoFI** Povi bsrI hpaII SCIFI caulI dsaV ncil hinfI maelli hhal/cfol hpall bsaWI acil hinPI **bsoFI** mcrI bbvI nspBII bsiEI

hinPI rmaI maeI haeIII/palI bslI

5101 ACAGGATTAG CAGAGCGAGG TAIGTAGGCG GIGCTACAGA GITCTIGAAG IGGIGGCCTA ACTACGGCTA CACTAGAAGG ACAGTATIG GIAICIGCGC IGICCIAAIC GICTCGCICC ATACAICCGC CACGAIGICI CAAGAACIIC ACCACCGGAI IGAIGCCGAI GIGAICIICC IGICAIAAAC CAIAGACGCG

hhaI/cfoI

bfaI

haeI

scfI

acil

mplI

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fnu4HI bsoFI bbvI acil acil cac8I CCGCTGGT AGCGGTGTTTTGTTTG CAAGCAGGGGGCGCCACAAAAAAAAAA	tru9I nlaIIII mseI rcaI maeII bspHI TCAGTGGA ACGAAAACTC ACGTTAAGGG ATTTTGGTCA AGGTCATTCCC TAAAACCAGT	I ATCTAAAG TATATATGAG TAAACTTGGT CTGACAGTTA TAGATTTC ATATATACTC ATTGAACCA GACTGTCAAT	pleI hinfI ahdI/eam1105I TGCCTGACTC CCGTCGTGT AGATAACTAC GATACGGGAG ACGGACTGAG GGGCACA TCTATTGATG CTATGCCCTC
F 43	sau3AI sau3AI mbol/ndeII[dam-] mbol/ndeII[dam-] hhal/cfol mbol/ndeII[dam-] dpnI[dam+] thal fuuDII/mvol dpnI[dam+] dpnI[dam+] bstUl bstVI/xhoII alwI[dam-] bsh1236I alwI[dam-] bstXI/xhoII 1 salwI[dam-] cGGGTCTGAC GCTCAGTGGA ACGAAAACTC TAATGCGCGT CTTTTTTCC TAGAGTTCTT CTAGGAAACT AGAAAAGATG CCCCAGACTG CGAGTCACCT TGCTTTTGA	sau3AI mbol/ndell[dam-] rma! hphi dpnl[dam+] sau3AI maeI tru9I mbol/ndell[dam-] msel dpnl[dam+] dpnll[dam-] tru9I bstYl/xhoII bstYl/xhoII msel alw[[dam-] bfaI ahaIII/draI ahaIII/draI ACTCTAATAC TTCACCTAGA TCCTTTTAAA TTAAAAATGA AGTTTTAAAT CAATCTAAAG TATAAAAATTTA ATTTTCTTAGATTTC ATAAAAATTC ATAAAAAATTC ATAAAAAATTC ATAAAAATTTC ATAAAAATTC ATAAAAAATTC ATAAAAAATTC ATAAAAAATTC ATAAAAAATTC ATAAAAAAAA	nlaIV sau3AI hgiCI mbol/ndeII[dam-] tru9I banI dpoi[dam+] msel mnli ddeI dpnII[dam-] foki ahdI/eam11 5501 CCAATGCTTA ATCAGTGAGG CACCTATCT AGCGATCTGT CTATTTCGTT CATCCATAGT TGCCTGACTC CCCG GGTTACGAAT TAGTCACTC GTGGATAGAG TCGCTAGACA GATAAAGCAA GTAGGTATCA ACGGACTGAG GGGC

ANTIBODY FRAGMENT-POLYMER CONJUGATES AND HUMANIZED

Appl. No.: 09/234,182

maeII

hhaI/cfoI

maeI

tru9I

sau96I

rmaI

hpall dsaV

Idsm ncil

SCLFI

hinPI

Atty Docket: GENENT.093A

mbol/ndell[dam-]

sau3AI

nlaIII

nlaIII

dpnII[dam-] maeIII alwI[dam-]

dpnII[dam-] dpnI[dam+]

mbol/ndell[dam-]

sau3AI

nlaIV

dpnI[dam+]

bsaWI Idsm

hhaI/cfoI sau96I hinPI haeIII/palI 5601 GGCTTACCAT CTGGCCCCAG TGCTGCAATG ATACCGCGAG ACCCACGCTC ACCGGCTCCA GATTTATCAG CAATAAACCA GCCAGCCGGA AGGGCCGAGC CCGAATGGIA GACCGGGGIC ACGACGITAC TAIGGCGCIC IGGGIGCGAG IGGCCGAGGI CIAAAIAGIC GITAITIGGI CGGICGGCCI ICCCGGCICG asuI hpall Idsm bglI cac8I pbmI/gsuI[dcm-] cfr101/bsrFI hphI nlaIV hpaII fauDII/mvaI bsh1236I bstul aciI haeIII/pall bsrDI fnu4HI **bsoFI** bbvI bsrI sau96I nlaIV asuI

bsmAI

bsaI

thaI

mstI psp1406I aviII/fspI CGICTICACC AGGACGIIGA AAIAGGCGGA GGIAGGICAG AIAAITAACA ACGGCCCIIC GAICTCAIIC AICAAGCGGI CAAITAICAA ACGCGIIGCA TGCGCAACGT 5701 GCAGAAGIGG ICCIGCAACI ITAICCGCCI CCAICCAGIC IAITAAIIGI IGCCGGGAAG CIAGAGIAAG IAGIICGCCA GIIAAIAGII tru9I bsrI mseI bfaI aluI caull asel/asnl/vspl mseI bsrI fokI mplI acil avall asuI

mslI cac81 scfi pstI fnu4HI bsoFI bbvI

ACAACGGIAA CGACGICCGI AGCACCACAG IGCGAGCAGC AAACCAIACC GAAGIAAGIC GAGGCCAAGG GIFGCIAGII CCGCICAAIG IACIAGGGGG 5801 IGTIGCCAIT GCIGCAGGCA ICGIGGIGIC ACGCICGICG IIIGGIAIGG CIICAIICAG CICCGGIICC CAACGAICAA GGCGAGIIAC AFGAICCCCC aluI hpaII maeIII sfaNI bsrDI bsgI

mbol/ndeII[dam-] mull dpnII[damdpnI[dam+] sau3AI

sau96I pvuI/bspCI bsiEI mcrI avall asuI

Enu4HI bsoFI bbvI

> nlaIII msll

haeIII/palI

eaeI

fau4HI aciI

bsoFI

GGTCCTCCGA TCGTTGTCAG AAGTAAGTTG GCCGCAGTGT TATCACTCAT GGTTATGGCA GCACTGCATA TACAACACGT TITITCGCCA ATCGAGGAAG CCAGGAGGCT AGCAACAGTC TTCATTCAAC CGGCGTCACA ATAGTGAGTA CCAATACCGT CGTGACGTAT cfrI 5901 ATGTTGTGCA AAAAAGCGGT TAGCTCCTTC aluI acil

ANTIBODY FRAGMENT-POLYMER CONJUGATES AND HUMANIZED

Hsei et al. Appl. No.: 09/234,182 Atty Docket: GENENT.093A

hphI

hphī

1 2002

bsiEI MCLI

bcgI

fpu4HI **bsoFI**

> rsaI scal

> > bsrI

fokI

nlaIII

acil

ddeI

TAAGAGAATG ACAGTACGGT AGGCATTCTA CGAAAAGACA CTGACCACTC ATGAGTTGGT TCAGTAAGAC TCTTATCACA TACGCCGCTG GCTCAACGAG ATGCGCCGAC CGAGTTGCTC 6001 ATTCTCTTAC TGTCATGCCA TCCGTAAGAT GCTTTTCTGT GACTGGTGAG TACTCAACCA AGTCATTCTG AGAATAGTGT maeIII hphI csp6I sfani

hinPI ahaII/bsaHI hinl1/acyI hgaI

fnuDII/mvnI hhaI/cfoI thaI

hpall

Idsm

SCLFI

ncil

mbol/ndeII[dam-]

sau3AI

dpnII[dam-] bstYI/xhoII

alwI[dam-]

nboli

asp700

XmpI

psp1406I

maelI

hgiAI/aspHI

bsp1286

dpnI[dam+]

tru9I bsh1236I bstuI acil

bsiHKAI bmyI mseI

caull hincil/hindli

dsav

ahaIII/draI

6101 TIGCCCGGCG TCAACACGCG ATAATACCGC GCCACATAGC AGAACTITAA AAGTGCTCAT CATIGGAAAA CGTICTICGG GGCGAAAACT CTCAAGGAIC AACGGGCCGC AGTTGTGCCC TALTATGGCG CGGTGTATCG TCTTGAAATT TTCACGAGTA GTAACCTTTT GCAAGAAGCC CCGCTTTTGA GAGTTCCTAG

mboII[dam-] eco57I sau3AI **bsp1286 bsiHKAI** bmyI

mbol/ndeII[dam-] tadI

bsrI

sau3AI

dpnII[dam-]

6201 TTACCGCTGT

nspBII

aciI

dpnI[dam+]

hgiAI/aspHI

sfaNI

mbol/ndell[dam-] dpnI[dam+] alw44I/snoI apaLI/snoI

dpnII[dam-] bssSI

TGAGAICCAG IICGAIGIAA CCCACICGIG CACCCAACIG AICIICAGCA ICTITIACII ICACCAGCGI IICIGGGIGA GCAAAAACAG maeIII alwI[dam-] bstYI/xhoII

AATGGCGACA ACTCTAGGTC AAGCTACATT GGGTGAGCAC GTGGGTTGAC TAGAAGTCGT AGAAAATGAA AGTGGTCGCA AAGACCCACT CGTTTTTGTC

mslI fpu4BI acil **bsoFI**

TGCCGCAAAA AAGGGAATAA GGGCGACACG GAAATGTTGA ATACTCATAC TCTTCCTTTT TCAATATTAT TGAAGCATTT ATCAGGGTTA CTICCGITIT ACGCCGITIT IICCCITAII CCCGCIGIGC CITIACAACI IAIGAGIAIG AGAAGGAAAA AGTIAIAATA ACTICGIAAA IAGICCCAAI earI/ksp632I 6301 GAAGGCAAAA

SapI

Iloqu

RAGMENT-POLYMER CONJUGATES AND HUMANIZED ANTI-IL-8 MONOCLONAL ANTIBODIES Hsei et al.

Atty Docket: GENENT.093A Appl. No.: 09/234,182



hinlI/acyI maeII

ahaII/bsaHI aatII ddeI

fnuDII/mvnI **bsh1236I** bstuI

hinPI

thaI

nlaIV hhaI/cfoI acil

bspHI acil bsmAI bsrBI

nlaIII rcal

AACAGAGTAC TCGCCTATGT ATAAACTTAC ATAAATCTTT TTATTTGTTT ATCCCCAAGG CGCGTGTAAA GGGGCTTTTC ACGGTGGACT GCAGATTCTT 6401 INGICICANG AGCGGATACA TATTIGAANG TATTIAGAAA AATAAACAAA TAGGGGITCC GCGCACATIT CCCCGAAAAG IGCCACCIGA CGICTAAGAA

haeIII/palI sau96I

IIoqu eco01091/drall asuI

bpuAI mnlI bssSI

> tru9I mseI

> > bspHI rcal

nlaIII

6501 ACCATTATTA TCATGACATT AACCTATAAA AATAGGCGTA TCACGAGGCC CTTTCGTCTT CAA TGGTAATAAT AGTACTGTAA TTGGATATTT TTATCCGCAT AGTGCTCCGG GAAAGCAGAA GTT bbsI

(SEQ:1D NO.61)

FIG. 411

Hsei et al.

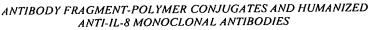
Appl. No.: 09/234,182 Atty Docket: GENENT.093A



>length: 6563

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1119 1195 1425 1434 1446 1512 1695 1696 1752 2155 2375 2727 3002 3090 3339 3463
                                                                                                                          2628 2781 2784 2787 2906 2926 3005 3045 3094 3141 3226 3241 3309 3342 3367 3412
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                                                   1093 1963 4449
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                                                                                                                                                                                                                                                                                                                              ahall/bsaHI(GRCGYC):
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 alw44I/snoI(GTGCAC):
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                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     apaLI/snoI(GTGCAC):
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         asp700(GAANNNTTC):
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           alwI[dam-](GGATC):
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          apyI[dcm+](CCWGG):
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      asp718(GGTACC):
                                                                                accIII (TCCGGA):
                           acc651(GGTACC):
                                                                                                                                                                                                                                                                             aflii(ACRYGT):
aatII(GACGIC):
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           apaI(GGGCCC):
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                apol (RAATTY):
                                                      accI (GTMKAC):
                                                                                                                                                                                                                                                                                                        ageI(ACCGGT):
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      asul(GGNCC):
                                                                                                          acil(CCGC):
                                                                                                                                                                                                                                                                                                                                                                                                                  aluI(AGCT):
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 aspHI
```

FIG. 41V



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Stop Template Primer

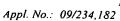
5' CAT GGT ATA GGT TAA ACT TAT TTA CAC 3' (SEQ ID NO.63) **SL.97.2**

NNS Randomization Primer

5' CAT GGT ATA GGT NNS ACT TAT TTA CAC 3' (SEQ ID NO.64) SL.97.3

FIG. 42

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Randomization of Position N35 of Variable Light Chain CDR-1 Amino Acid Frequency

Phage Display (NNS Codon Library) Sort #3	ay (NNS Co	don Libra	ry) Sort #3
Amino Acid	Frequency % Total	% Total	IC50 (nM)
Asparagine (wt)	1	5.6	4.9
Glycine	9	16.6	3.1
Aspartic Acid	3	16.6	3.1
Glutamic Acid	4	22.2	0.1
Alanine	2	5.6	0.2
Jysine		5.6	N
Serine	1	1.9	N

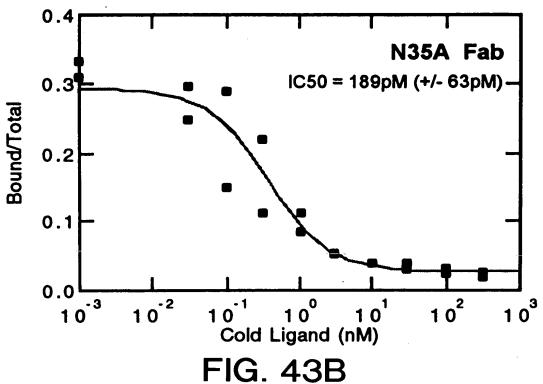
FIG. 43A

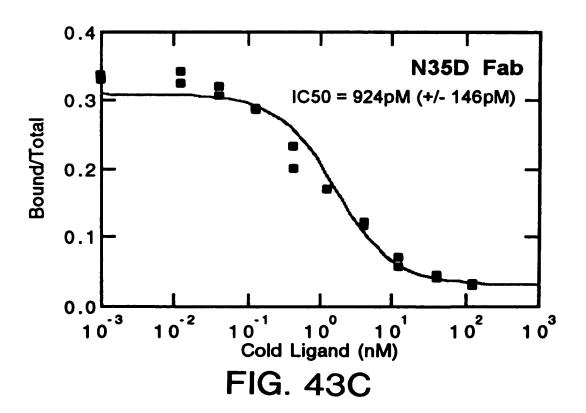


<u>.</u>;

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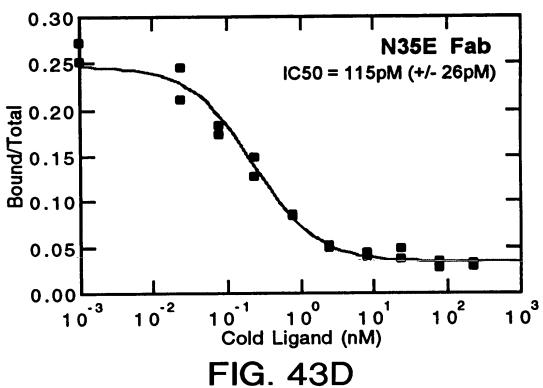
Atty Docket: GENENT.093A Appl. No.: 09/234,182

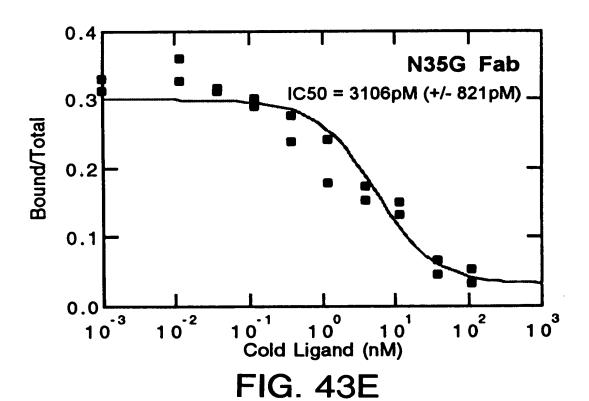




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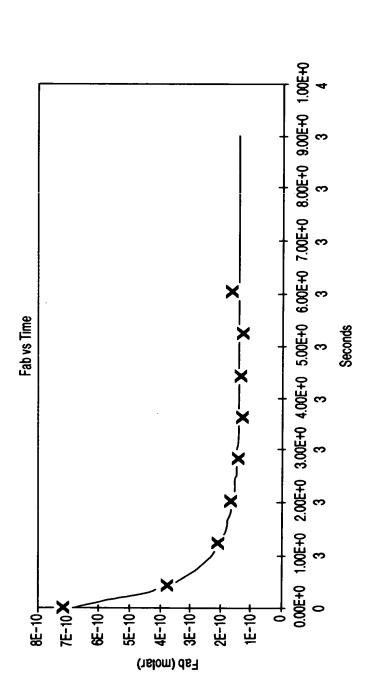


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Representative Conc versus Time Plot. Shown is the kinetic data for 6G4V11N35A.F(ab')2.

		_	
Kd	114pM	109pM	54pM
kd	ON.	2.1x10 ⁻⁴	2.6x10 ⁻⁴
ka	Q	$2.0x10^6$	4.7×10 ⁶
SAMPLE	6G4V11N35A-Fab	6G4V11N35A-F(ab') ₂	6G4V11N35E-Fab

FIG. 44

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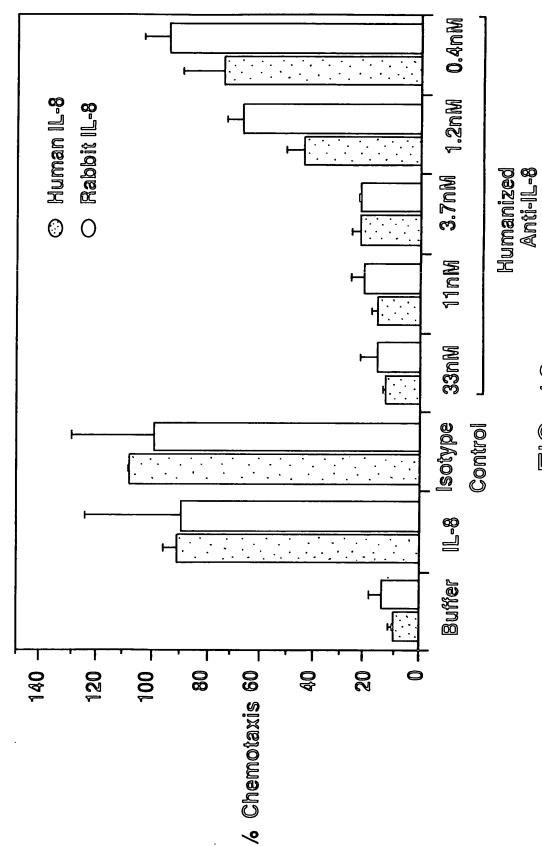
1					TTTTTTCTAT	
					AAAAAAGATA	
	M K K N					
	CGTATGCGAC	TATAGGTCTA	CTGGGTCAGG	GGCTCGAGGG	TGTCCGCCTC ACAGGCGGAG	ACACCCGCTA
	A Y A D					
121					ATGGTATAGG TACCATATCC	
18	R V T I	T C R	S S O	S L V H	G I G	ETY
181					TACTGATTTA ATGACTAAAT	
38	L H W Y				L I Y	
241					GTTCTGGGAC	
58	N R F S				S G T	D F T
301					ATTACTGTTC TAATGACAAG	
78					Y C S	
361					TCAAACGAAC AGTTTGCTTG	
98	H V P L					V A A
421					AATCTGGAAC	
118					TTAGACCTTG S G T	
481					TACAGTGGAA	
138					ATGTCACCTT Q W K	
541					AGGACAGCAA TCCTGTCGTT	
158	A L Q S			V T E Q		D S T
601					ACGAGAAACA	
178	ATGTCGGAGT Y S L S			TTTCGTCTGA K A D Y	TGCTCTTTGT E K H	GTTTCAGATG K V Y
661					CAAAGAGCTT GTTTCTCGAA	
198	A C E V	T H Q	G L S	S P V T	K S F	N R G
721					CTAGTACGCA GATCATGCGT	
218) ID NO.62)	1GCGGCC1GC	GTAGCACCGG	GATCATGCGT	IGNICAGENT

FIG. 45



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5'-CTAGTGCAGTCTGGCGGTGGCCTGGTGCAGCCAGGGGGCTCACTCCGTTTGTCCTGTGCAGCTTCTGGCTACTCCTTC-3' (SEQ ID NO.66) N35AH1upr

5'-TCGAGAAGGAGTAGCCAGAAGCTGCACAGGACAAACGGAGTGAGCCCCCTGGCTGCACCAGGCCACCGCCAGACTGCACT (SEQ ID NO.67)

N35AH1Mr

Bold indicates nucleotide change destroying Pvull site.



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>This has the pSVI backbone with the pRK7 cloning linker (pSVI7) and the intron DHFR(ID) >made from pSVI.WTSD.D by adding a linearization linker(LL) into the Hpal site > length: 8120 (circular)

cacel

aluI

BBtI

TTCGAGCTCG CCCGACATTG ATTATTGACT AGAGTCGATC GACAGCTGTG GAATGTGTGT CAGTTAGGGT GTGGAAAGTC CCCAGGCTCC CCAGCAGGCA AAGCTCGAGC GGGCTGTAAC TAATAACTGA TCTCAGCTAG CTGTCGACAC CTTACACACA GTCAATCCCA CACCTTTCAG GGGTCCGAGG GGTCGTCGGT cacel apyI[dcm+] nlaIV ecoRII BCLFI batni deav bsaJI mvaI DBMFI mbol/ndell[dam-] nspBII sau3AI aluI IInad taqI[dam-] pleI dpnII[dam-] dpnI[dam+] pvul/bspCI taqI[dam-] bsiEI ncrI hinfi bfal maeI rmaI hgiAI/aspHI ec1136II 1 TTCGAGCTCG **bsp1286 DBIHKAI** hgiJII banII bmyI sacI taqī

CTTCATACGT TTCGTACGTA GAGTTAATCA GTCGTTGGTC CACACCTTTC AGGGGTCCGA GGGGTCGTCC GTCTTCATAC GTTTCGTACG TAGAGTTAAT CAGCAACCAG GTGTGGAAAG TCCCCAGGGT CCCCAGCAGG CAGAAGTATG CAAAGCATGC ATCTCAATTA nsil/avallI nspHI cac8I Idsu sfani Ppu10I nlaIII cac8I apyI[dcm+] bsmFI nlaIV ecoRII BCLFI bsaJI **b**stNI mval dsaV apyI[dcm+] ecoRII SCIFI dsav betNI mvaI sexAI GAAGTATGCA AAGCATGCAT CTCAATTAGT nsil/avallI sfani ppu10I nlaIII IHdsu cacel sphI Idsu 101

acil bsaJI ncol bell deal acil bsrI acil acil acil foki acil **DamFI**

201

nlaIII

styI

FIG. 48A

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rmaI

7

haelli/pall mcri eagl/xmalli/eclXI eael cfri bsiEI mspl hpall ATCCGG	nlaIII CATGGT GTACCA G^	rsal csp61 scal CAAGTACTTC
aluI rmaI maeI bfaI nheI cac8I aluI CAAAAAGCTA GCTTI	fnu4HI bsoFI bbvI nspBII aciI nlacccGCTG CCATCA TAGGGGCGAC GGTAGT	real xmnI cap(asp700 scaI GGAACGAGTT CAAGTAC
maer styr bsajr blnr avrir[dam-] haeII/palr stur haer mnlr bfar TTTGGAGGCC TAGGCTTTTG	fnu4HI bsoFI rsal csp6I scfI mnlI aciI nlaIII GTACCGCCTA TAGAGGATA AGAGGATTTT ATCCCGCTG CCATCATGGT CATGCCGCAT TCTCCTAAA TAGGGGCGAC GGTAGTACCA	
mnli mnli bseRI AGAAGTAGTG AGGAGGCTTT	maeII maeIII AGTGACGTAA TCACTGCATT	bsmai bsai GGGATTGGCA AGAACGGAGA
fnu4HI bsofi bsofi bsofi bsofi bsofi sfil bacill/pall haeill/pall bsofi mnli alul mnli bsofi avilicam-lanci mnli bsofi avilicam-lanci mnli bsofi avil mnli alul mnli bsofi avilicam-lanci mnli bsofi avil nacilicam-lanci mnli bsofi avil mnli alul mnli bsofi avil haei mnli bsofi avil haeili/pall bsofi avil haei mnli bsofi avil alul haeili/pall bsofi avil haei mnli bsofi avil alul haeili/pall bsofi alul haei and alul haeili/pall alul haeili/pall bsofi avil alul haei and avilicación avilicación avilication containce avilicación avilication containce avilication av	tfil scrFI hinfI ncil acil mspI thaI hpaII fnuDII/mvnI dsav bstUI cauII bsh1236I 401 CCGGAACGG TGCATTGGAA CGCGGATCC GGCCTTGCC ACGTAACCTT GCGCCTAAGG GGCACGGTTC	haeIII/palI haeI scrFI mvaI bsrBI ecoRII dsaV pflMI bsnAI apyI[dcm+] taqI sfaNI bsnFI bsnFI 501 TCGACCATTG AACTGCACAG GGTTTTATAAC CCCTAACCGT TCTTGCCTCT GGAGGCGAGT AGCTGGTAAC TTGACGTAGC GGAGGCGAGT
hael mnli } 301 TATGCAGAGG C ATACGTCTCC G	scrFI nc1I mspI hpaII dsav cauII 401 CCGGAACGG T	taqI 501 TCGACCATTG A AGCTGGTAAC T

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foki sfaNi msel

bstXI

haeIII/palI

haeI

mvaI

scrFI

SCLFI

mvaI

ecoRII

ecoRII

dsav

701 AGGACAGAAT TAATATAGTT CTCAGTAGAG AACTCAAAGA ACCACCAGGA GGAGCTCATT TTCTTGCCAA AAGTTTGGAT GATGCCTTAA GACTTATTGA TCCTGTCTTA ATTATATCAA GAGTCATCT TGGAGTGCTT CTGAATAACT CTGAATAACT

bslI bseRI

asel/asnl/vspl





SCLFI

tru9I mseI	ahalii/drai CCTTTAA GGAAATT									H	
tf1I hinfI	ddel mboll tagl c TGAGAAGAAT CGA G ACTCTTCTTA GCT								tru9I	aflII/bfrI	
mval cecoRII dsaV bstNI apyI[dcm+]	mnli dagi mboli tagi ahali CAAAGAATGA CCACAACCTC TTCAGTGGAA GGTAAAACAGA ATCTGGTGAT TATGGGTAGG AAAACCTGGT TCTCCATTCC TGAGAAGAAT CGACCTTTAA GTTTCTTACT GGTGTTGGAG AAGTCACCTT CCATTTGTCT TAGACCACTA ATACCCATCC TTTTGGACCA AGAGGTAAGG ACTCTTCTTA GCTGGAAATT			ipHI							
	AT TATGGGTAG TA ATACCCATC	sstI	hgiJII	hgiAI/aspHI	ecl136II	bsp1286	bsiHKAI	DmyI	mnll aluI	bssSI banII	
tfiI hinfI hphI	alwNI[dcm-] GGTAAACAGA ATCTGGTG CCATTTGTCT TAGACCAC									seq	
eco57I mboII earl/ksp632I	mnli ccrc trcagregaa egag aagreacetr									ddeI	
υ	mnli dagi mboli tagi ahali soli caaagaarga ccacaaccr trocatrca acacaacra sexal del mboli tagi ahali: 601 caaagaarga ccacaaccr trocatrca tragaagaar cgaccrtraa grincitaca ccacarccr ccattrorcatr ccattrorcatra aracccarcc tittrogacca aggregaccr ccattrorcatra aracccarcc tittrogacca aggregactra gergaaaarr								tru9I	mseI	

FIG. 48C

TGTTGGCCTT AACCGTTCAT TTCATCTGTA CCAAACCTAT CAGCCTCCGT CAAGACAAAT GGTCCTTCGG TACTTAGTTG GTCCGGTGGA ATCTGAGAAA 801 ACAACCGGAA TTGGCAAGTA AAGTAGACAT GGTTTGGATA GTCGGAGGCA GTTCTGTTTA CCAGGAAGCC ATGAATCAAC CAGGCCACCT TAGACTCTTT

hinfI ddel pleI

hinfl apyl[dcm+]

apy1[dcm+]

mplI

accI nlaIII

mspi hpali bsaWI

bstNI

nlall tfil

bstNI

dsaV

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mnlI

sfaNI

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ahaII/bsaHI SCLFI

hinl1/acy1

hgaI

Mnll mvaI

ecoRII

ecoNI bstNI dsav

ball ddeI apyI[dcm+] bsaJI

mnlI

mn]I

GTGACAAGGA TCATGCAGGA ATTTGAAAGT GACACGTTTT TCCCAGAAAT TGATTTGGGG AAATATAAAC CTCTCCCAGA ATACCCAGGC GTCCTCTCTG

CACTGTTCCT AGTACGTCCT TAAACTTTCA CTGTGCAAAA AGGGTCTTTA ACTAAACCCC TTTATATTTG GAGAGGGTCT TATGGGTCCG CAGGAGACAC

afllII

mbol/ndell[dam-]

nlaIII

maeIII

apoI

maeIII alwI[dam-]

901

dpnII[dam-]

dpnI[dam+]

CORII SCLFI dsav mvaľ

apyI[dcm+] bstNI

sau96I

avall

Iloqu accI sfaNI mnll asuI

1001 AGGTCCAGGA GGAAAAAGGC ATCAAGTATA AGTTTGAAGT CTACGAGAAG AAAGACTAAC AGGAAGATGC TTTCAAGTTC TCTGCTCCCC TCCTAAAGCT TCCAGGTCCT CCTTTTCCG TAGTTCATAT TCAAACTTCA GATGCTCTTC TTTCTGATTG TCCTTCTACG AAAGTTCAAG AGACGAGGGG AGGATTTCGA I I oqu *END DHFR

bsaJI sau3AI mbol/ndeII[dam-] dpnII[dam-] dpnI[dam+]

nlaIII

styl ncol

ppu10I

alwI[dam-]

asel/asnl/vspl

tru9I msel

fnu4HI

bsoFI

DbvI

cac8I dsaI bsmFI

1101 AIGCAITITI AIAAGACCAI GGGACTITIG CIGGCTITAG AICCCCTIGG CITCGITAGA ACGCAGCIAC AAITAAIACA TAACCITAIG IAICAIACAC TACGTAAAAA TATTCTGGTA CCCTGAAAAC GACCGAAATC TAGGGGAACC GAAGCAATCT TGCGTCGATG TTAATTATGT ATTGGAATAC ATAGTATGTG bstYI/xhoII bsaJI nsil/avallI

sau96I avall asuI

SCLFI

ecoRII mvaI

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ecoRI	tagI apoI	clal/bsp106	hspDI[dam-]	1201 ATACGATITA GETGACACTA TAGATAACAT CCACTITGCC TITCTCTCCA CAGGTGTCCA CICCCAGGTC CAACTGCACT TCGGTTCTAT CGATIGAATT TATGATATA CCATAGAAAT CCACAGATA GCTAACTIAA TATGCTAAAT CCACAGATA GCTAACTIAA	7111.
		mnlI	bsaJI	GCACC TCGG	SVH: CLA-A
dsaV	bstNI	apyI[dcm+]	bsli bsaJi	TCCCAGGTC CAACT AGGGTCCAG GTTGA	sed from pRK6G4Z5VH: Cla-Avril
			llad	CCA CAGGIGICCA C	ω.
				C TTTCTCT G AAAGAGA	
				CCACTTTGC	
			fokī	AGATAACAT TCTATTGTA	
		maeIII	hoh! scf!	GGTGACACTA T	
				01 ATACGATTI	
				7	

	bral nael bbvi alul acil haelil/pali acaactica ccrecreca reference refreact ccarcacte acaccac ccaccact E V Q L V Q S G G L V Q serfi
rmaI maeI	bial alui SA GCTAGTGCAG ST CGATCACGCC T C V Q
rsal	bpml/gsul(dcm-) bsrl csp61 AACTGCAACT GGAGTACATT CAGAAGTTC TTGACGTTGA GTCTTCAAG TTGACGTTGA CCTCATGTAA GTCTTCAAG
rmaI	mael bfal TTCTAGTAGC AAGATCATCG
nlaIII styI pflMI ncoI dsaI	bell foki nael bpml/gsul[dcm-] bial nael bbv. bsaji nlaili foki bfal bsri csp6i alul acii haelil/pali 1301 CCACCATGGG ATGGTCATCTTTTTTTAGTAGC AACTGCAACT GGAGTACATT CAGAAGTTCA GCTAGTGCAG TCTGGCGGTG GCCTGGTGCA GGTGGTACCC TACCAGTACA TAGTAGGAAA AAGATCATCG TTGACGTTGA CCTCATGTAA GTCTTCAAGT CGATCACGTC AGACCGCCAC CGGACCACGT 1 1 E V Q L V Q S G G L V Q scrFI

				님				scrFI	mvaI	ecoRII	dsaV	bstNI	bslI	apyI[dcm+]	haeIII/palI	196nas	eco01091/drall	l asul	A GGCCTGGAA	r cccggacctr	n E		
ncil	Idsm	dsaV	Caull	xmaI/pspAI	Smal	SCLFI	ncil	dsav	Cauli	bsli	bsaJI	avaI bs	bsaJI	sau961 ap	nlaIV haeI	asuI haeIII/palI	IV asul bell e	eco01091/drall	GICCGICAGG CCCCGGGIA	CAGGCAGTCC GGGGCCCATI	V R Q A P G K		
														1961s	avall	a6	nla	bsrI	TATGCACTGG	ATACGTGACC	X H		
													pleI	hinfi	tagI	xhoI	paeR71	aval maelil	TACTCCTTCT CGAGTCACTA	ATGAGGAAGA GCTCAGTGAT	YSFSSHY	FIG. 48E	
														aluI	alwNI[dcm-]	fnu4HI	bsoFI	bbvI	TGTCCTGTGC AGCTTCTGGC	ACAGGACACG TCGAAGACCG	SCAASG		
									hqiJII	bep1286	I/mq	BCTFI	mval banii	ecoRII	deav	batni	baaJI	apvI[dcm+]	1401 GCCAGGGGG TCACTCCGTT	CGGTCCCCC AGTGAGGCAA ACAGGACACG TCGAAGACCG ATGAGGAAGA GCTCAGTGAT ATACGTGACC CAGGCAGTCC GGGGCCCATT CCCGGACCTT	14 P G G S L R L		

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thal foudil/mvol foudil/mvol foudil/mvol foudil/mvol soubsil betul betul soubsil soubsil behilds behild behild benild behilds beal nrul ordingst ataatcaaaa GTTCAAGGGC CGTTTCACTT TATCTCGCGA CAACTCCAAA AACACAGTAACCA TATTAGTTTT CAAGTTCCCG GCAAAGTGAA ATAGAGCGCT GTTGATGCTT TTGTGTCTT AACACTCAAAGTGAAAAAAAAAA	hinll/acyl ahall/basHl bsrl aatll maelll taql hph mooll maell CAATGGTGAC TGGTTCTTCG ACGTCTGGG GTTACCACTG ACCAGAAGC TGCAGACCCC N G D W F F D V W G	scrFI mvaI mvaI ecoRII dsav bstNI bsaJI sau96I haeIII/palI asuI tl bspl286 bspl286 bspl286 bspl286 acil bsaJI bmyI mnlI bmyI nspBII apyI[dcm crcchAcAcAcCCC CTCTCGCGC crccACACACCCC crccACACACCCCC crccACACACCCCC crccACACACCCCC crccACACACCCCC crccACACACCCCC crccACACACCCCC crccACACACCCCC crccACACACCCCC crccACACACCCCC crccCCCCCCCCCC
haelii/pali sau96i asul ataatcaaaa GTTCAAGGC CGTTTCACTT TATTAGTTTT CAAGTTCCG GCAAAGTGAA	mnli CTATTACTGT GCAAGAGGGG ATTATCGCTA GATAATGACA CGTTCTCCCC TAATAGCGAT Y Y C A R G D Y R Y	sau96I sau96I nlaIV hgiJII nlaIV bsp1286 banI p120I bmyI mvaI nII mboII ecoRII uI mboII bstNI bseRI bsaJI asuI bbsI apyI[dcm+] mnlI 11 eco01091/draII bsaJI mnlI ccaag GGCCCATCGG TCTTCCCCT GGCACCTCC T GGTTC CCGGGTAGCC AGAAGGGGGA CCGTGGGAGG A K G P S V F P L A P S S
bslr sau3AI mbol/ndeIl[dam+] dpnl[dam+] alwl[dam-] alwl[dam-] cCATCGAT ATATTGATCC TTCCAN CCACCTA TATAACTAGG AAGGTT V G Y I D P S N	beti beti bati cac8i ddel drdi ifol Accrecagar GAACAGCCTG CGTGCTGAGG ACACTGCCGT CTATTACTGT GCAAGAGGGG ATTATCGCTA CAATGGTGAC TGGTTCTTCG ACGTCTGGGG TGGACGTCTA CTTGTCGGAC GCACGACTCC TGTGACGGGC ATTATCCC TAATAGCGAT GTTACCACTG ACGTCTGGGG TGACGTCTA CTTGTCGGAC GCACGACTCC TGTGACGGCA GATAATGACA CGTTCTCCCC TAATAGCGAT GTTACCACTG ACGACACCCC TGACGTCTA CTTGTCGGAC GCACGACTCC TGTGACGGCA GATAATGACA CGTTCTCCCC TAATAGCGAT GTTACCACTG ACCAAGAAGC TGCAGAACCCCC TGACGTCTA CTTGTCGGAC GCACGACTCC TAATAGCGAT GTTACCACTG ACCAAGAAGC TGCAGAACCCCC TGACGTCTA CTTGTCGGAC GCACGACACCCCC TGACGTCTA CTTGTCGGAC GCACGACACACACACACACACACACACACACACA	Sau961
1501 TG AC 47 W	1601 Ab	1701 TC

TRACE!

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ahdI/eam1105I

sau96I

avall

SCFFI

asuI

mvaI

1801 CTGGGCTGCC TGGTCAAGGA CTACTTCCCC GAACCGGTGA CGGTGTCGTG GAACTCAGGC GCCCTGACCA GCGGCGTGCA CACCTTCCCG GCTGTCCTAC GACCCGACGG ACCAGITCCI GAIGAAGGGG CIIGGCCACI GCCACAGCAC CIIGAGICCG CGGGACIGGI CGCCGCACGI GIGGAAGGGC CGACAGGAIG hpall ddel hhal/cfol nspBII alw441/snol cauII Idsm SCLFI ncil dsaV T F P acil apaLI/snoI **bsp1286** hgiAI/aspHI G V H bmyI cac8I **beiHKAI** fnu4HI **bsoFI** တ A L T ahaII/bsaHI hinl1/acyI haeII hgici narI banI S S nlaIV kasī ageI tth11111/aspI cfr101/bsrFI E P V T hphI hpall Idsm bsaWI maeIII bsll Y F P V K D apyI[dcm+] ecoRII ecoNI bstNI dsav bslI I G C L fnu4HI bsoFI bbvI 147

hinPI

SCLFI mvaI

1901 AGTOCTCAGG ACTOTACTOC CTCAGCAGOG TGGTGACTGT GCCCTCTAGC AGCTTGGGCA CCCAGACCTA CATCTGCAAC GTGAATCACA AGCCCAGCAA TCAGGAGTCC TGAGATGAGG GAGTCGTCGC ACCACTGACA CGGGAGATCG TCGAACCCGT GGGTCTGGAT GTAGACGTTG CACTTAGTGT TCGGGTCGTT hinfI maeII z U bfal alul bsp1286 nlaIV hgici banI bmyI bsoFI hphi bmyi mnli bbvi rmaI bsp1286 maeI P S S Λ Τ Λ maeIII fnu4HI bsoFI mnll bbvI bsu361/mstII/sauI ddeI

mnll hinfI

eco811

S

ddeI pleI

fnu4HI

bbsI mnlI 2001 CACCAAGGIG GACAAGAAAG TIGAGCCCAA ATCTIGIAC AAAACTCACA CAIGCCCACC GIGCCCAGCA CCIGAACTCC IGGGGGGACC GICAGTCTIC GIGGTICITIC AACTCGGGII TAGAACACTG ITTIGAGIGI GIACGGGIGG CACGGGICGI GGACTIGAGG ACCCCCCIGG CAGICAAGA bpuAI nlaIV DSMFI apyI[dcm+] bsaJI ecoRII bstNI dsav E I bmyI alwNI[dcm-] CPA **bsp1286** nlaIII nspHI Idsu maeIII Ω ပ တ E P **bsp1286** hgiJII banll bmyI T K V bsaJI

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bbsI bsu361/mstII/sauI 2101 CTCTTCCCC CAAAACCCAA GGACACCCTC ATGATCTCCC GGACCCCTGA GGTCACATGC GTGGTGGTGG ACGTGAGCCA CGAAGACCCT GAGGTCAAGT recacreger gerreregea crecagrica GIGGICAGCG ICCICACCGI CACCAGTCGC AGGAGTGGCA fnu4HI hqaI mnlI drdI mnlI bpuAI eco811 mboll ddel A S A A E D P CACGIACCGI GTGCATGGCA csp6I ഗ rsal maell T maeII bsaAI 2201 TCAACTGGTA CGTGGACGGC GTGGAGGTGC ATAATGCCAA GACAAAGCCG CGGGAGGAGC AGTACAACAG CACAAGGGGG GITITGGGII CCIGIGGGAG IACIAGAGGG CCIGGGGACI CCAGIGIACG CACCACCACC GCCCTCCTCG TCATGTTGTC ຜ X - csp6I rsaI asuI bsu361/mstII/sauI nlaIII IHdsu Idsu bseRI fnuDII/mvnI स स mnlI mslI eco811 maeIII sacII/sstII T A **bsh1236I** nspBII bstUI fnu4HI thaI bsaJI kspI bsoFI dsaI acil CIGITICGGC E E T X P mbol/ndell[dam-] sau96I nlaIV avall hpall dpnII[dam-] Idsm rcal dpn1[dam+] SCLFI caulI dsaV ncil AGTIGACCAI GCACCIGCCG CACCICCACG IAITACGGIT S N A K msli bspHI[dam-] sau3AI nlaIII mnlI mn]I bsaJI styl Ö Ω maeII bsrI bsaAI earl/ksp6321 csp6I ecoRII SCLFI mvaI dsav ¥ IIoqu

bsoFI bbvI GTACAAGTGC AAGGTCTCCA ACAAAGCCCT CCCAGCCCCC ATCGAGAAAA CCATCTCCAA AGCCAAAGGG TGTTTCGGGA GGGTCGGGG TAGCTCTTTT GGTAGAGGTT TCGGTTTCCC A taqi MnlI X A CATGITCACG ITCCAGAGGI bsmAI K V S bsaI Y csp6I rsaI 2301 CCTGCACCAG GACTGGCTGA ATGGCAAGGA GGACGTGGTC CTGACCGACT TACCGTTCCT × ecoNI bstNI bsrI apyI[dcm+] bell

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ANTIBODY FRAGMENT-POLYMER CONJUGATES AND HUMANIZED

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hpall

ncil Idsm

nlalv mboli scfl cac8I 2401 CAGCCCCGAG AACCACAGGT GTACACCCTG CCCCCATCCC GGGAAGAGAT GACCAAGAAC CAGGTCAGCC TGACCTGCCT GGTCAAAGGC TTCTATCCCA 2501 GCGACATCGC CGTGGAGTGG GAGAGCAATG GGCAGCCGGA GAACAACTAC AAGACCACGC CTCCCGTGCT GGACTCCGAC GGCTCCTTCT TCCTCAAG CTCTCGTTAC CCGTCGCCCT CTTGTTGATG TTCTGGTGCG GAGGGCACGA CCTGAGGCTG CCGAGGAAGA AGGAGATGTC GICGGGGCTC TIGGIGICCA CAIGIGGGAC GGGGGIAGGG CCCTICICIA CIGGITCIIG GICCAGICGG ACIGGACGGA CCAGIIICCG AAGAIAGGGI Ilum IIoqm sapI × > apy1[dcm+] bstNI ecoRII DSPMI hinfi SCLFI dsaV apyI[dcm+] nsil/avallI nlaIII ecoRII ppu10I SCLFI batNI sexAI mvaI deav mnlI earI/ksp632I E E E N bsaJI mboII Ilodm xmaI/pspAI bpuAI xmnI bbsI maeII cauli dsav caulI bsp14071/bsrGI bslI avaI SCLFI dsav smaI ncil P S R hpall O P E Idsm fokI fnu4HI bsoFI bslI bbvI fnu4HI **bsoFI** S bsrDI Y T L csp6I rsal CGCTGTAGCG GCACCTCACC > E mall baaJI dsaI bell dsaI hphI

347

GTTCGAGTGG CACCTGTTCT CGTCCACCGT CGTCCCCTTG CAGAAGAGTA CGAGGCACTA CGTACTCCGA GACGTGTTGG TGATGTGCGT CTTCTCGGAG

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V D K

K L

2601 CAAGCTCACC GTGGACAAGA GCAGGTGGCA GCAGGGGAAC GTCTTCTCAT GCTCCGTGAT GCATGAGGCT CTGCACAACC ACTACACGCA

sfaNI mull

nlaIII

asp700

Lydd IMqsd

aluI bsaJI

eari/ksp632I

GAAGAGCCTC

ANTIBODY FRAGMENT-POLYMER CONJUGATES AND HUMANIZED

Hsei et al.

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sau96I

agggacagag gcccatttac tcacgctgcc gggatctcag ctggacgtct tcgaaccggc ggtaccgggt tgaacaaata acgtcgaata ttaccaatgt s l s p g k o (SEQ ID NO.11) maelll TGCAGCTTAT AATGGTTACA fnu4HI bsoFI bbvI 2701 TCCCTGTCTC CGGGTAAATG AGTGCGACGG CCCTAGAGTC GACCTGCAGA AGCTTGGCCG CCATGGCCCA ACTTGTTTAT haeIII/pall asuI bsoFI nlaIII aluI haeIII/palI hindili bqll bsaJI dsaI ncol styl fnu4HI acil sfiI cfrI eaeI mael hincil/hindil pstI begI asul bfal acci bspMI taqi rmal sall sau96I hinfI pleI haeIII/palI hpall BCLFI caulI dsav ncil nspi SISP **DBMAI** belI 447

nlaIII alwI[dam-] 2801 AATAAAGCAA TAGCATCACA AATTTCACAA ATAAAGCATT TTTTTCACTG CATTCTAGTT GTGGTTTGTC CAAACTCATC AATGTATCTT ATCATGTCTG ttatttegtt atcgtagtgt ttaaagtgtt tatttegtaa aaaaagtgae gtaagateaa caccaaaeag gtttgagtag ttacatagaa tagtacagae csp6I nlaIV rsal kpnI maeI bfal bsmI haeI bsoFI styI fnu4HI sfaNI apol mbol/ndeIl[dam-] taqI[dam-] tru9I clal/bsp106[dam-] bspDI[dam-] mseI

dpnII[dam-]

pvuI/bspCI

beiEI mcrl

dpnI[dam+]

sau3AI

FIG. 48,

CTAGCTAGCC CTTAATTAAG CCGCGTCGTG GTACCGGACT TTATTGGAGA CTTTCTCCTT GAACCAATCC ATGGAAGACT CCGCCTTTCT TGGTAGACAC

GATCGATCGG GAATTAATTC GGCGCAGCAC CATGGCCTGA AATAACCTCT GAAAGAGGAA CTTGGTTAGG TACCTTCTGA

GCCGGAAGA ACCATCTGTG

ddeI aciI mplI

acc65I asp718

mnlI

mn]I

dsal haeIII/palI

ncol

bbvI hinPI

XanI

sau3AI

hhal/cfol nlallI

bsaJI

dpnII[dam-] asel/asnI/vspI

2901

dpn1[dam+] asp700 mbol/ndeII[dam-]

hgici

banI

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sfaNI ppulOI nsil/avalII nsil/avalII sphI sphI nspHI cac8I sac8I sAGTATGCA AAGCATGCAT CTCAATTAGT CAGCA. TTCATAGT TTCGTACGTA GAGTTAATCA GTCGT STCAGCAACC ATAGTCCCGC CCCTAACTCC GCCCA. SAGTCGTTGG TATCAGGGC GGGATTGAGG CGGGT fnu4HI bsoFI bsoFI bsoFI sfiI mnli mnli ddeI haeIII/palI bsaJI mnli aluI

FIG. 48K

ANTIBODY FRAGMENT-POLYMER CONJUGATES AND HUMANIZED ANTI-IL-8 MONOCLONAL ANTIBODIES Hsei et al. Appl. No.: 09/234,182 Atty Docket: GENENT.093A

mbol/ndeII[dam-] dpnI[dam+] dpnII[dam-] alwI[dam-]

sau3AI



						H	pleI	hinfi	CCGTGCCAAG AGTCAGGTAA	Ul matched splice donar
		tfil	hinfi	acii	thaI	fnuDII/mvnI	bstUI	bsh1236I	GCGCGATTCC	Ul match
			IXI						TGCATTGGAA	
scrFI ncil mspI hpaII	dsaV haeIII/palI	mcrI	eagl/xmalll/eclXI	eaeI	cfrI	bsiEI	mspI cauli	hpall	TATCCGG CCGGGAACGG ATAGGCC GGCCCTTGCC	^seq from pSVI6B5-6G4VL: AvrII - HindIII frag
		aluI	rmal	maeI	bfal	nheI	cac8I	aluI	AAAAAGCTA GCT	B5-6G4VL: Avr
rmaI	maeI styI	bsaJI	blai	avrII[dam-]	haeIII/palI	stuI	haeI	mnli bfal	3301 AGGAGGCTTT TTTGGAGGCC TAGGCTTTTG CAAAAAGCTA GCTTATCCGG CCGGGAACGG TGCATTGGAA CGCGGATTCC CCGTGCCAAG AGTCAGGTAA TCCTCCGAAA AAACCTCCGG ATCCGAAAAC GTTTTTCGAT CGAATAGGCC GGCCCTTGCC ACGTAACCTT GCGCCTAAGG GGCACGGTTC TCAGTCCATT	`seg from pSVI6
								mnlI	3301 AGGAGGCTTT TCCTCCGAAA	

							fokI	GACAT	CTGTA	
	[-E				ı			ACACT	TGTGA	
Jam-J	clal/bsp106[dam-]	lam-]		mbol/ndeII[dam-]	[+1	[-ex	-	CCTACTO	AGGATGAC	ខ្
tadi(dam-)	laI/bg	bspDI[dam-]	sau3AI	oI/nde	dpnI[dam+]	dpnII[dam-]	lwI[dam-]	rc gan	AG CT2	ved AT
•	΄υ΄	Ã	SBI	q	ďр	ф	alw]	AGGCCCACCC CCTTGGCTTC GTTAGAACGC GGCTACAATT AATACATAAC CTTTTGGATC GATCCTACTG ACACTGACAT	TCCGGGTGGG GGAACCGAAG CAATCTTGCG CCGATGTTAA TTATGTATTG GAAAACCTAG CTAGGATGAC TGTGACTGTA	^removed ATG
							bsh1236I aseI/asnI/vspI	CATAAC	FGTATTG	
					ru9I	mseI	eI/ası	T AAT	A TTA	
					fnuDII/mvnI tru9I	E	[a.8	PACAAT	ATCTTA	
	fpu4HI	bsoFI	acil	thaI	uDII/a	bstui	h12361	C GGCJ	7900 S	er
	44	Д	ਕ	ţ	fn	pg	ps	TAGAACG	ATCTTGC	^sp6 promoter
								TC GT	AG CA	^sp6
					styI	_	bsaJI	CTTGGC	3GAACCG	
				bstXI	• •	I/pal]	~	ACCC (rege o	
				.gq	sau96I styl	haeIII/palI	asuI	AGGCCC	TCCGGG	
					scfI	pleI	hinfi	GTACCGCCTA TAGAGTCTAT	LATGGCGGAT ATCTCAGATA	
						-41	ofI 1	TA TAC	AT ATC	
					acil	I.	cspéI scfI hinfI	ACCGCC	reces	
						I.B.	leo Cel)1 GT	ฮี	

3401

IgG vH natural lariat restored^

lariat consensus^ ^U2 match

ANTIBODY FRAGMENT-POLYMER CONJUGATES AND HUMANIZED ANTI-IL-8 MONOCLONAL ANTIBODIES Hsei et al. Appl. No.: 09/234,182 Atty Docket: GENENT.093A

hgiJII hgiAI/aspHI ec1136II bsp1286

aluI sstI sacI



nlaIII styI	pflMI ncol	ecoRI apol	dam-j Trgaattc caccatggga Aacttaag gtggtaccct
	clal/bsp106 sfaNi	fnu4HI bsoFI taqI	DDV1 DSPU1[dam-] GGGCTGCATC GATTGAAT CCCGACGTAG CTAACTTA
rmal mael bfal		bstUI cac8I bsh1236I aluI	bsaji nrui alui GCACC TCGGTTCGCG AAGCTAGCTT CGTGG AGCCAAGCGC TTCGATCGAA
sau96I avali asul scrFl mval	ecorii daav	bstNI apyI[dcm+]	badi bani bevildam.j bani 3501 CCACTTTTC TTTTTCTCCA CAGGTGTCCAGGTC CAACTGCACC TCGGTTCGCG AAGCTAGCTT GGGCTGCATC GATTGAATTC CACCATGGGA GGTGAAAAAG AAAAGGGT GTCCACAGGT GAGGGTCCAG GTTGACGTGG AGCCAAGCGC TTCGATCGAA CCCGACGTAG CTAACTTAAG GTGGTACCCT

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bsinkai	bemFI bmyI			ည	ပ္တ	U	
				CTG	GAC	DIO MIOS PSS LSA SVGD	
		mull		ŭ	S A	S	
		Ē	acil	GTCCGC	CAGGCG	Æ	
						တ	
				ដូ	GGA	H	
		bsrI avaI	II	CIC	GAG	တ	
			pI ban	CCCGAG	GGGCTC	တ	
						Д	
			/88	E.	ક	Ø	
			tth1111/aspI banII	TCTAGTAGCA ACTGCAACTG GAGTACATTC AGATATCCAG ATGACCCAGT CCCGAGCTC CCTGTCCGCC TCTGTGGGCG	AGATCATCGT TGACGTTGAC CTCATGTAAG TCTATAGGTC TACTGGGTCA GGGGCTCGAG GGACAGGCGG AGACACCCGC	œ	
						H	
			Ĭ	AT	ŢĀ	Σ	
				SES	GIC	a	
)RV	PATC	TAG	H	
			ecoRV	AGA1	ICT.	Д	
		-		ဥ	AG		
	rsaI	<pre>pbmI/gsuI[dcm-]</pre>	berl csp6I	CAT	GTA		
				AGT	Ş		
			н	ig ig	ັບ ບ		
		ďq	ber	ACT	'TGA		
				IGC.	\CG1		
				AC.	ŢĞ		
				SCA	CGI		
	H	H	H	GTA	CAT		
	rmaI	maeI	bfal	CTA	AGAT		
					-		
				CIT	GAA		
			fokI	ATC	TAG		
			J L	J.	P AG		
			nlaIII	1601 TGGTCATGTA TCATCCTTTT	ACCAGTACAT AGTAGGAAAA		
			nl	TCA	AGT		
				Ę	ğ		
				601		7	
				m			

mvaI	ecoRII	dsav	bstNI aluI	apyI[dcm+]	3701 ATAGGGTCAC CATCACCTGC AGGTCAAGTC AAAGCTTAGT ACATGGTATA GGTGCTACGT ATTTACACTG GTATCAACAG AAACCAGGAA AAGCTCCGAA	PAICCCAGTG GTAGTGGACG TCCAGTTCAG TTTCGAATCA TGTACCATAT CCACGATGCA TAAATGTGAC CATAGTTGTC TTTGGTCCTT TTCGAGGCTT	SSOSLV HGI GATY LHW YQQ KPGKAPK
				bsrI	ATTTACACTG	TAAATGTGAC	L H
		maell	snaBI	bsaAI	GGTGCTACGT	CCACGATGCA	GATY
	н		19	nlaIII	ACATGGTATA	TGTACCATAT	H G I
pstI	rsaI	ddeI	aluI csp6I	hindIII nlaIII	AAAGCTTAGT	TTTCGAATCA	SLV
	begI	88e8387I	DspMI	MI	AGGTCAAGTC 1	TCCAGTTCAG	R S S O
				hphI bspMI	CATCACCTGC	GTAGTGGACG	I I C
		hphI	maeIII	bstEII	ATAGGGTCAC	TATCCCAGTG	18 RVT ITCR
					3701		18

BcfI

FIG. 48M



ANTIBODY FRAGMENT-POLYMER CONJUGATES AND HUMANIZED Hsei et al.

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fnu4HI haeIII/palI bsoFI bbvI mbol/ndeII[dam-] fnu4HI scfI pstI bsgI bsoFI bbvI 3801 ACTACTGATT TACAAAGTAT CCAATCGATT CTCTGGAGTC CCTTCTCGCT TCTCTGGATC CGGTTCTGGG ACGGATTTCA CTCTGACCAT CAGCAGTCTG GTOGGTCTTC TGAAGCGTTG AATAATGACA AGTGTCTCAT GAGTACAGGG CGAGTGCAAA CCTGTCCCAT GGTTCCACCT CTAGTTTGCT TGACACCGAC GATCAAACGA ACTGTGGCTG TVAAA TGATGACTAA ATGTTTCATA GGTTAGCTAA GAGACCTCAG GGAAGAGCGA AGAGACCTAG GCCAAGACCC TGCCTAAAGT GAGACTGGTA GTCGTCAGAC haeI ဟ S dpnII[dam-] dpnI[dam+] I I I K R sau3AI 3901 CAGCCAGAAG ACTICGCAAC TIAITACIGI TCACAGAGIA CICAIGICCC GCICACGIII GGACAGGGIA CCAAGGIGGA 臼 asp700 Œ Iumx > Ω banI bsaJI kpnI styI asp718 csp6I **DSMFI** acc65I cac8I hgici nlaIV rsal Ħ v v dpnII[dam-] ഗ a bstYI/xhoII dpnI[dam+] alwI[dam-] alwI[dam-] ט nlaIV bamHI maell LT asp700 bsrBI acil XmnI **DSMFI** ч у nlaIII bpmI/gsuI[dcm-] ρ, csp6I **bsmFI** scal rsaI S bspDI[dam-] hinfI pleI a clal/bsp106 ຜ hinfI tagI ပ Y Y Ā

mbol/ndell[dam-]

hpall bslI

bsaWI sau3AI

Idsm

4001 CACCATCTGT CTTCATCTTC CCGCCATCTG ATGAGCAGTT GAAATCTGGA ACTGCTTCTG TTGTGTGCCT GCTGAATAAC TTCTATCCCA GAGAGGCCAA

CTTTAGACCT TGACGAAGAC AACACGGA CGACTTATTG AAGATAGGGT CTCTCCGGTT

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GTGGTAGACA GAAGTAGAAG GGCGGTAGAC TACTCGTCAA

mbolI acil

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bpuAI IIoqu

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bbsI

IIodm bpuAI bbsI

mnlI

Hsei et al.

opl. No.: 09/234,182 Atty Docket: GENENT.093A



4301 GAGAGTGTTA AGCTTGGCCC CCATGCCCCA ACTTGTTTAT TGCAGCTTAT AATGGTTACA AATAAAGCAA TAGCATCACA AATTTCACAA ATAAAGCCATT CTCTCACAAT TCGAACCGGC GGTACCGGGT TGAACAAATA ACGTCGAATA TTACCAATGT TTATTTCGTT ATCGTAGTGT TTAAAGTGTT TATTTCGTAA 4201 CTGACGCTGA GCAAAGCAGA CTACGAGAAA CACAAAGTCT ACGCCTGCGA AGTCACCCAT CAGGGCCTGA GCTCGCCCGT CACAAAGAGC TTCAACAGG GTGTTTCAGA TGCGGACGCT TCAGTGGGTA GTCCCGGACT CGAGCGGGCA GTGTTCTCG AAGTTGTCCC 4101 AGTACAGTGG AAGGTGGATA ACGCCCTCCA ATCGGGTAAC TCCCAGGAGA GTGTCACAGA GCAGGACAGC AAGGACAGCA CCTACAGCCT CAGCAGCACC GGATGTCGGA GTCGTCGTGG fuu4HI ddeI bsoFI bbvI scfI mull aluI S maeIII sfaNI apol TAGCCCATTG AGGGTCCTCT CACAGTGTCT CGTCCTGTCG TTCCTGTCGT SPV hgiAI/aspHI ec113611 ddeI cac8I **bsp1286** eco01091/drall **DBIHKAI** hgiJII haeIII/pall sau96I aluI asul banil **DmyI** sstI sacI alwNI[dcm-] maeIII maeIII maeIII hphI F > apyI[dcm+] 3 0 8 ecoRII fnu4HI **b**stNI cac8I bsoFI scrFI dsaV maeIII bsaJI mvaI bbvI acci H K V Y z U haeIII/palI တ GATGCTCTTT TICCACCIAT IGGGGAGGI Bau96I O I 田 asuI bell mnll bsoFI nlaIII aluI haeIII/palI bsaJI deal sfil styl hindili bqli ncol fnu4HI acil GACTGCGACT CGTTTCGTCT K A D cfrI eael blpI/bpull02I cell1/espI tru9I mseI LTLS TCATGTCACC 3 0 2 hgaI csp61 rsal 151

FIG. 480

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apyI [dcm+]

bstNI dsaV

ecoRII

SCLFI

mvaI

bemFI nlaIV

bsaJI



mbol/ndell[dam-]

sau3AI

dpnII[dam-] dpnI[dam+]

pvuI/bspCI

tagI[dam-]

bsiEI BCLI

dsal haeIII/palI 4401 TITITCACIG CAITCIAGIT GIGGITIGIC CAAACICAIC AAIGIAICII AICAIGICIG GAICGAICGG GAAITAAIIC GGCGCAGCAC CAIGGCCIGA aaaaagtgac gtaagatcaa caccaaacag gtttgagtag ttacatagaa tagtacagac ctagctagcc cttaattaag ccgcgtcgtg gtaccggact haeI hhal/cfol nlallI bsaJI ncol bsoFI styI fnu4HI bbvI hinPI dpnII[dam-] aseI/asnI/vspI bspDI[dam-] tru9I mseI clal/bsp106[dam-] asp700 ^sv40 mbol/ndell[dam-] dpnI[dam+] xmnI nlaIII alwI[dam-] sau3AI mael rmai bfal DemI

TTATTGGAGA CITTCICCIT GAACCAAICC AIGGAAGACI CCGCCITICI IGGICGACAC CITACACACA GICAAICOCA CACCITICAG GGGICCGAGG sfani sfaNI

4501 AATAACCTCT GAAAGAGAA CITGGTTAGG TACCTTCTGA GGCGGAAAGA ACCAGCTGTG GAATGTGTGT CAGTTAGGGT GTGGAAAGTC CCCAGGCTCC

nspBII IInad aluI

acil

acc65I asp718

mn]I

moli

mnll ddeI

csp6I

nlaIV

hgici kpnI banI

rsaI

nsil/avallI 4601 CCAGCAGGCA GAAGTAIGCA AAGCAIGCAI CICAAITAGI CAGCAACCAG GIGIGGAAAG ICCCCAGGCI CCCCAGCAGG CAGAAGIAIG CAAAGCAIGC ppu10I nlaIII cacel apyI[dcm+] bsmFI nlaIV ecoRII SCIFI bsaJI bstNI dsav mvaI apyI[dcm+] ecoRII BCLFI bstNI dsaV mval sexAI nsil/avallI ppu10I nlaIII nspHI cacel nspī sphī

nspHI

Idgu

cac8I

GGTCGTCCGT CTTCATACGT TTCGTACGTA GAGTTAATCA GTCGTTGGTC CACACCTTTC AGGGGTCCGA GGGGTCGTCC GTCTTCATAC GTTTCGTACG

cac8I

OCT 2 1 2002

ANTIBODY FRAGMENT-POLYMER CONJUGATES AND HUMANIZED ANTI-IL-8 MONOCLONAL ANTIBODIES

Atty Docket: GENENT.093A

maeIII

mnll bfaI

bseRI

haeI stuI

nlalII

styl ncol dsaI

TAGAGTTAAT CAGTCGTTGG TATCAGGGCG GGGATTGAGG CGGGTAGGGC GGGGATTGAG GCGGGTCAAG GCGGGTAAGA GGCGGGGTAC CGACTGATTA CCGCCCCATG GCTGACTAAT acil bsaJI 4701 ATCTCAATTA GTCAGCAACC ATAGTCCCGC CCCTAACTCC GCCCATCCCG CCCCTAACTC CGCCCAGTTC CGCCCATTCT acil bsrI acil acil fokl bsmFI

acil

acil

avrII[dam-] haeIII/palI mael rmaI bsaJI styl blnI

fnu4HI

bsoFI

bglI

mpli aluI haeIII/pall Mnll sfil mnlI

haeIII/palI haeIII/pall bsaJI mnlI

mnli bsaJI acil

CCGAGGCCGC CTCGGCCTCT GAGCTATTCC AGAAGTAGTG AGGAGGCTTT TTTGGAGGCC TAGGCTTTTG CAAAAAGCTG AAAAAATAA ATACGTCTCC GGCTCCGGCG GAGCCGGAGA CTCGATAAGG TCTTCATCAC TCCTCCGAAA AAACCTCCGG ATCCGAAAAC GTTTTTCGAC start pUC118^ 4801 TTTTTTTT TATGCAGAGG

scfI fnuDII/mvnI hhal/cfol hinPI bstul eagl/xmalil/eclXi thal hinPI haeIII/palI

eaeI

fnu4HI

mcrl

ahaIII/draI tru9I msel tru91 bsh12361 msel hhaI/cfoI cac8I ascI tru9I paci berBI bsoFI paeR7I bsiEI xhoI fnu4HI cfrI aval bsoFI notI

bspMI

pstI

4901 TIACCTCGAG CGCCGCTTA ATTAAGGCGC GCCATTTAAA TCCTGCAGGT AACAGCTTGG CACTGGCCGT CGTTTTACAA CGTCGTGACT GGGAAAACCC AATGGAGCTC GCCGCCGAAT TAATTCCGCG CGGTAAATTT AGGACGTCCA TTGTCGAACC GTGACCGGCA GCAAAATGTT GCAGCACTGA CCCTTTTGGG maell maelll berI aluI sse8387I msel bssHII swal mnll acil acil

apyI[dcm+]

bsaJI

bstNI

dsav

haeIII/palI

cfrI eaeI

bsgI maeIII

ecoRII

BCLFI

mvaI

Alinearization linker inserted into Hpal site

FIG. 480

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ACCECAATGE GITCAAITAG CEGAACETCE TETAGEGEGE AAGCGGTCGA CCGCATTAIC GCTTCTCCGG GCGTGGCTAG CGGGAAGGGT TGTCAACGCA 5001 TGGCGTTACC CAACTTAATC GCCTTGCAGC ACATCCCCCC TTCGCCAGCT GGCGTAATAG CGAAGAGGCC CGCACCGATC GCCCTTCCCA ACAGTTGCGT mbol/ndeII[dam-] dpnII[dam-] dpnI[dam+] pvuI/bspCI sau3AI bsiEI mcrI haelil/pall mplI acil ear1/ksp6321 sau96I mbolI cac8I asuI cac8I nspBII aluI IInad cac8I fokI fnu4HI bsoFI bbvI tru9I mseI

fnuDII/mvnI bstUI scfI rsal hhal/cfol 5101 AGCCTGAATG GCGAATGGCG CCTGATGCGG TATTTTCTCC TTACGCATCT GTGCGGTATT TCACACCGCA TACGTCAAAG CAACCATAGT ACGCGCCTG TCGGACTTAC CGCTTACCGC GGACTACGCC ATAAAAGAGG AATGCGTAGA CACGCCATAA AGTGTGGCGT ATGCAGTTTC GTTGGTATCA TGCGCGGAC **bsh1236I** bslI hinPI csp6I maeII aciI acil sfaNI acil sfaNI ahaII/bsaHI hhaI/cfoI hinl1/acy1 nlaIV hgici haeII narI kası banI

hinPI

maeIII

hhaI/cfoI bsrBI acil bfal cac8I hinPI hinPI haeII rmal haeII maeI hhaI/cfoI cac8I acil maeIII bbvI maeIII fnuDII/mvnI hhaI/cfoI fnu4HI **bsh1236I** bsoFI hinPI bstUI fnuDII/mvnI msel bshl236I hhaI/cfoI bsoFI bstul tru9I aciI thaI hhal/cfol hinPl hinPI fnu4HI **DBOFI** acil

acil

fnu4HI

I DOGI



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5301 TITCICGCCA CGIICGCCGG CIIICCCCGI CAAGCICIAA AICGGGGGCI CCCIIIAGGG IICCGAIIIA GIGCIIIACG GCACCICGAC CCCAAAAAC tagI banI mnlI hgici nlaIV nlaIV **bsp1286** banII bmyI aluI cfr101/bsrFI cac8I maeII

nlaIV hgiJII

hpall Idsm

AAAGAGCGGT GCAAGCGGCC GAAAGGGGGCA GTTCGAGATT TAGCCCCCGA GGGAAATCCC AAGGCTAAAT CACGAAATGC CGTGGAGCTG GGGTTTTTTG 5401 TIGATITIGG IGAIGGITCA CGIAGIGGG CAICGCCCIG AIAGACGGII ITICGCCCTI IGACGIIGGA GICCACGIIC ITIAAIAGIG GACICIIGIT AACTAAACCC ACTACCAAGT GCATCACCCG GTAGCGGGAC TATCTGCCAA AAAGCGGGAA ACTGCAACCT CAGGTGCAAG AAATTATCAC CTGAGAACAA hinfI tru9I mseI hinfI maeII maeII pleI haeIII/pall sau96I asuI draIII bsaAI hphI

tru9I 5501 CCAAACTGGA ACAACACTCA ACCCTATCTC GGGCTATTCT TTGATTTAT AAGGGATTTT GCCGATTTCG GCCTATTGGT TAAAAAATGA GCTGATTTAA mseI TGTTGTGGGT TGGGATAGAG CCCGATAAGA AAACTAAATA TTCCCTAAAA CGGCTAAAGC CGGATAACCA ATTTTTTACT CGACTAAATT aluI tru9I msel haeIII/palI bslI avaI bslI GGTTTGACCT

hgiAI/aspHI

tru9I mseI fnu4HI aciI bsoFI sfaNI alw441/snol csp61 rsaI apaLI/snoI ddeI bsp1286 **DSIHKAI** bmyI psp1406I maell tru9I mseI SSpl apol tru91 msel bstUI msel fnuDII/mvnI **bsh1236I** thaI tru9I

GIGCACTCIC AGIACAAICI GCICIGAIGC CGCAIAGIIA AGCCAACICC gititiaaat tececttaaa attetittat aattecaaat ettaaaatac caceteagag teatettaga cgagactace ecetateaat tegetteage 5601 CAAAATTTA ACGCGAATTT TAACAAAATA TTAACGTTTA CAATTTTATG

CGATAGCGAT GCACTGACCC AGTACCGACG CGGGGCTGTG GGCGGTTGTG GGCGACTGCG CGGGACTGCC CGAACAGACG AGGGCCGTAG GCGAATGTCT 5701 GCTATCGCTA CGTGACTGGG TCATGGCTGC GCCCCGACAC CCGCCAACAC CCGCTGACGC GCCCTGACGG GCTTGTCTGC acil hgal acil

TCCCGCCATC CGCTTACAGA

caull acil

drdI

nspBII bsh1236I

nlaIII hhaI/cfoI

bsaAI tthllll/aspI bbvI

maeII bsrI maeIII

hinPI

fnu4HI

bsoFI

bstul

dsaV fokI

sfaNI

hpall

BCLFI

fnuDII/mvnI

hhal/cfol

thaI

hinPI

ncil

Idsm

FIG. 48S

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haeIII/palI eco01091/drall 5801 CAAGCTGTGA CCGTCTCCGG GAGCTGCATG TGTCAGAGGT TTTCACCGTC ATCACCGAAA CGCGCGAGGC AGTATTCTTG AAGACGAAAG GGCCTCGTGA GITCGACACT GGCAGAGGCC CICGACGIAC ACAGICICCA AAAGIGGCAG IAGIGGCIITI GCGCGCICCG ICAIAAGAAC IICIGCIIIC CCGGAGCACI asuI basSI Bau96I mbol I bpuAI ppsI fnuDII/mvnI fnuDII/mvnI hhaI/cfoI bsh1236I thal mull **bsh12361** bstul hinPI bstul hphI hphI mnlI bell cauli alui nlaili nspHI nspI fnu4HI **bsoFI PPVI** hpall scrFI ncil Idsm dsaV maeIII bsmAI esp3I bemBI

fnuDII/mvnI **bsh1236I** acil bstul thaI

nlaIV

hhaI/cfoI hinPI ddeI maeII aatII IHdsq msel

ahaII/bsaHI

nlaIII

rcal

tru9I

hinl1/acyI

TITATAGGIT AAIGICAIGA TAATAAIGGI IICITAGACG ICAGGIGGCA CITITICGGG AAAIGIGCGC GGAACCCCIA IIIGIITAII GAAAAGCCCC TTTACACGCG CCTTGGGGAT AAACAAATAA ATGCGGATAA AAATATCCAA TTACAGTACT ATTATTACCA AAGAATCTGC AGTCCACCGT 5901 TACGCCTATT

rcal

6001 TITCTAAATA CATTCAAATA TGTATCCGCT CATGAGACAA TAACCCTGAT AAATGCTTCA ATAATATTGA AAAAGGAAGA GTATGAGTAT TCAACATTTC earI/ksp632I Ilodm Sapl bsmAI acil nlaIII bspHI bsrBI

msll

hgiAI/aspHI AAAGATTTAT GTAAGTTTAT ACATAGGCGA GTACTCTGTT ATTGGGACTA TTTACGAAGT TATTATAACT TTTTCCTTCT CATACTCATA AGTTGTAAAG

bsp1286 **DSIHKAI**

mbol/ndell[dam-]

sau3AI

alw44I/snoI apaLI/snoI dpn1[dam+] bmy1 6101 CGTGTCGCCC TTATTCCCGTT TTTTGCGGCA TTTTGCCTTC CTGTTTTTGC TCACCCAGAA ACGCTGGTGA AAGTAAAAGA TGCTGAAGAT CAGTTGGGTG dpnII[dam-] sfaNi mboli[dam-] eco57I hphI hphI fnu4HI **bsoFI** acil

48

GCACAGCGGG AATAAGGGAA AAAACGCCGT AAAACGGAAG GACAAAAACG AGTGGGTCTT TGCGACCACT TTCATTTTCT ACGACTTCTA GTCAACCCAC

NTI-IL-8 MONOCLONAL ANTIBODIES

Atty Docket: GENENT.093A

mbol/ndeII[dam-]

haeIII/pall

sau3AI

1 2002

GIGCICACCC AAIGIAGCII GACCIAGAGI IGICGCCAII CIAGGAACIC ICAAAAGCGG GGCIICTIGC AAAAGGIIAC IACICGIGAA AAITICAAGA 6201 CACGAGIGGG TIACAICGAA CIGGAICICA ACAGCGGIAA GAICCIIGAG AGIITICGCC CCGAAGAACG IITICCAAIG AIGAGCACII IIAAAGIICI ahaIII/draI bsp1286 tru9I bsiHKAI mseI hgiAI/aspHI bmyI psp1406I maelI asp700 Iumx Iloqu mbol/ndell[dam-] dpnII[dam-] alwI[dam-] dpnI[dam+] acil bstYI/xhoII mbol/ndell[dam-] bsrI dpnII[dam-] alwI[dam-] bstYI/xhoII dpnI[dam+] maeIII taqI

sau3AI

nspBII

sau3AI

scal hphi maelli berI csp6I rsaI ddeI fnu4HI acil bsiEI bsoFI mcrI bcqI ahaII/bsaHI hpall hinll/acyI hgal cauli ncil Idsm dsaV fnuDII/mvnI hha1/cfo1 **bsh1236I** acil thaI bstuI hinPI

SCLFI

6301 GCTATGTGGC GCGGTATTAT CCCGTGATGA CGCCGGCQA GAGCAACTCG GTCGCCGCAT ACACTATTCT CAGAATGACT TGGTTGAGTA CTCACCAGTC CGATACACCG CGCCATAATA GGGCACTACT GCGCCCCGTT CTCGTTGAGC CAGCGGCGTA TGTGATAAGA GTCTTACTGA ACCAACTCAT GAGTGGTCAG

dpnII [damdpnI[dam+] pvul/bspCI **bsiEI** mcrI fnu4HI cfrI eaeI **bsoFI** acil bbvi msli nlali fnu4HI bsoFI

6401 ACAGAAAAG ATCTTACGGA TGGCATGACA GTAAGAGAAT TATGCAGTGC TGCCATAACC ATGAGTGATA ACACTGCGGC CAACTTACTT CTGACAACGA TGTCTTTTCG TAGAATGCCT ACCGTACTGT CATTCTCTTA ATACGTCACG ACGGTATTGG TACTCACTAT TGTGACGCCG GTTGAATGAA GACTGTTGCT nlaIII

nlaIII

fokI

sfaNI

mbol/ndell[dam-] aluI hpaII dpnII[dam-] bsaWI nlaIV dpnI[dam+] sau3AI mbol/ndeII[dam-] sau3AI maeIII dpnII[dam-] dpnI[dam+] nlaili alwi [dam-] acil aluI sau96I avall asuI mnll

6501 TCGGAGGACC GAAGGAGCTA ACCGCTTTTT TGCACAACAT GGGGGATCAT GTAACTCGCC TTGATCGTTG GGAACCGGAG CTGAATGAAG CCATACCAAA AGCCTCCTGG CTTCCTCGAT TGGCGAAAAA ACGTGTTGTA CCCCCTAGTA CATTGAGGGG AACTAGCAAC CCTTGGGCTC GACTTACTTC GGTATGGTTT

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tru9I

mseI

ahaIII/draI

maeIII

tru9I

mseI

banI mnlI

dpnII[dam-]

dpnI[dam+]

hgici

nlaIV

ddeI

sau3AI

mbol/ndeII[dam-]

tru9I mseI



asel/asnl/vspl **bsmAI** bsal 6701 GACTGGATGG AGGCGGATAA AGTTGCAGGA CCACTTCTGC GCTCGGCCCT TCCGGCTGGC TGGTTATTG CTGATAAATC TGGAGCCGGT GAGCGTGGGT CTCGCGGTAT CATTGCAGCA CTGGGGGCCAG ATGGTAAGCC CTCCCGTATC GTAGTTATCT ACACGACGGG GAGTCAGGCA ACTATGGATG AACGAAATAG 6601 CGACGAGCGT GACACCACGA TGCCAGCAGC AATGGCAACA ACGTTGCGCA AACTATTAAC TGGCGAACTA CTTACTCTAG CTTCCGGGCA ACAATTAATA CTGACCTACC TCCGCCTATT TCAACGTCCT GGTGAAGACG CGAGCCGGGA AGGCCGACCG ACCAAATAAC GACTATTAG ACCTCGGCCA CTCGCACCCA GCTGCTCGCA CIGTGGTGCT ACGGTCGTCG TTACCGTTGT TGCAACGCGT TTGATAATTG ACCGCTTGAT GAATGAGATC GAAGGGCCGT TGTTAATTAT GAGGGCCATA GTAACGICGI GACCCCGGIC TACCAIICGG GAGGCAIAG CAICAAIAGA IGIGCIGCCC CICAGICGI IGAIACCIAC IIGCIIIAIC tru91 mseI cfr101/bsrFI bpmI/gsul[dcm-] nlaIV hphI hpall Idsm fokI hpaiiIdsm SCLFI dsaV cauII ncil aluI rmal maeI bfal ahdi/eam1105i hinfI bsrI tru9I mseI cac8I hpaII Idsm haeIII/palI hhal/cfol avili/fspI sau96I hinPI bglI asaI mstI hhaI/cfoI psp1406I mae_I] hinPI Ilum haeIII/palI cac8I bsrDI sau96I avalI asuI fnu4HI **bsoFI** sfaNI bbvI I96nes nlaIV berI asuI fnu4HI bsoFI bbvI acil bsh1236I bsrDI mslI maeIII fnuDII/mvnI mnlI fokI acil bstul thal 6801

mbol/ndeII[dam-] dpnII[dam-] dpnI[dam+] sau3AI TITAAAAGGA TCTAGGTGAA GATCCTTTTT GATAATCTCA TGACCAAAAT CCCTTAACGT GAGTTTTCGT TCCACTGAGC GTCAGACCC GTAGAAAAGA 6901 ACAGATCGCT GAGATAGGTG CCTCACTGAT TAAGCATTGG TAACTGTCAG ACCAAGTTTA CTCATATATA CTTTAGATTG ATTTAAAACT TCATTTTAA TGTCTAGGGA CTCTATCCAC GGAGTGACTA ATTCGTAACC ATTGACAGTC TGGTTCAAAT GAGTATATAT GAAATCTAAC TAAATTTTGA AGTAAAATT ddeI maeII tru9I mseI nlaIII bspHI rcal mbol/ndeII[dam-] dpnII[damdpnI[dam+] alwI[dam-] bstYI/xhoII ahaiii/drai bfai mboii[dam-] sau3AI mbol/ndeII[dam-] sau3AI hphI dpnII[dam-] tru9I betYI/xhoII dpnI[dam+] alwI[dam-] maeI rmaI mseI 7001

GGGAATTGCA CTCAAAAGCA AGGTGACTCG CAGTCTGGGG CATCTTTTCT AAATTTTCCT AGATCCACTT CTAGGAAAA CTATTAGAGT ACTGGTTTTA



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mbol/ndell[dam-] aluI dpnII[dam-] dpnI[dam+] alwi[dam-] GITTGITTGC CGGATCAAGA AGTITCCTAG AAGAACTCTA GGAAAAAAAG ACGCGCAITA GACGACGAAC GITIGITITI ITGGTGGCGA TGGTC3CCAC CAAACAAACG GCCTAGITCI sau3AI hpaII mspl TGCGCGTAAT CTGCTGCTTG CAAACAAAA AACCACCGCT ACCAGCGGTG nspBII acil acil cac8I fnu4HI **bsoFI** bbvI fnuDII/mvnI **bsh1236I** hhaI/cfoI bstul hinPI mbol/ndell[dam-] thal 7101 TCAAAGGATC TTCTTGAGAT CCTTTTTTTC dpnII[dam-] dpnII[dam-] alwI[dam-] bstYI/xhoII dpnI[dam+] mbol/ndeII[dam-] mboll[dam-] bstYI/xhoII dpnI[dam+] alwI[dam-]

sau3AI

7201 GCTACCAACT CITITICCGA AGGTAACTGG CTICAGCAGA GCGCAGATAC CAAATACTGT CCTICTAGTG TAGCCGTAGT TAGGCCACCA CTICAAGAAC CGATGCTTGA GAAAAAGGCT TCCATTGACC GAAGTCGTCT CGCGTCTATG GTTTATGACA GGAAGATCAC ATCGGCATCA ATCCGGTGGT GAAGTTCTTG haeIII/palI haeI bslI maeI bfaI hhaI/cfoI hinPI eco57I bsrI maelll

rmaI

| fnu4HI | SCIFI | bSOFI | DEVI | | DE

pleI hinfi

AGACATCGTG GCGGATGTAT GGAGCGAGAC GATTAGGACA ATGGTCACCG ACGACGGTCA CCGCTATTCA GCACAGAATG GCCCAACCTG AGTTCTGCTA 7301 TCTGTAGCAC CGCCTACATA CCTCGCTCTG CTAATCCTGT TACCAGTGGC TGCTGCCAGT GGCGATAAGT CGTGTCTTAC CGGGTTGGAC TCAAGACGAT

mnli

acil

alw44I/snoI hgiAI/aspHI apaLI/snoI bsp1286 **DSIHKAI** bmyI hinPI bsiEI bbvI mcrI nspBII hhal/cfol Enu4HI bsoFI hpaII Idsm bsaWI maelil

TICGIGCACA CAGCCCAGCT IGGAGCGAAC GACCIACACC GAACIGAGAI ACCIACAGCG 7401 AGTTACCGGA TAAGGCGCAG CGGTCGGGCT GAACGGGGGG TTCGTGCACA CAGCCCAGCT TGGAGCGAAC GACCTACACC GAACTGAGAT ACCTACAGG TCAATGGCCT ATTCCGCGTC GCCAGCCCGA CTTGCCCCCC AAGCACGTGT GTCGGGTCGA ACCTCGCTTG CTGGATGTGG CTTGACTCTA TGGATGTCGC

aluI

scfI

ddeI

FIG. 48W

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scrFI

mvaI

aluI apyI[dcm+] ecoRII betNI dsav bsaJl 7501 TGAGCATTGA GAAAGCGCCA CGCTTCCCGA AGGGAGAAAG GCGGACAGGT ATCCGGTAAG CGGCAGGGTC GGAACAGGAG AGCGCACGAG GGAGCTTCCA ACTCGTAACT CTTTCGCGGT GCGAAGGGCT TCCCTCTTTC CGCCTGTCCA TAGGCCATTC GCCGTCCCAG CCTTGTCCTC TCGCGTGCTC CCTCGAAGGT CCIGGIAICI TIAIAGICCI GICGGGIITC GCCACCICIG ACTIGAGOGI CGAITITIGI GAIGCICGIC AGGGGGGGGG AGCCIAIGGA 7701 AAACGCCAG CAACGCGGCC TTTTTACGGT TCCTGGCCTT TTGCTGGCCT TTTGCTCACA TGTTCTTTCC TGCGTTATCC CCTGATTCTG TGGATAACCG TTTTGCGGTC GTTGCGCCGG AAAAATGCCA AGGACCGGAA AACGACCGGA AAACGAGTGT ACAAGAAAGG ACGCAATAGG GGACTAAGAC ACCTATTGGC CCCCTTTGC GGACCATAGA AATATCAGGA CAGCCCAAAG CGGTGGAGAC TGAACTCGCA GCTAAAAACA CTACGAGCAG TCCCCCCGCC TCGGATACCT nlaIV hinPI mnll hhaI/cfoI bssSI hinfI tfil fnu4HI **bsoFI** acil tagI aflIII nspHI haeIII/palI nspI hgaI hpall nlallI bell bsaWI mnli drdI haeI cac81 acil haeIII/palI apyI[dcm+] mval bsll ecoRII nlaIV haeI bstNI SCLFI dsaV haeIII/palI fnuDII/mvnI hhaI/cfoI thal bslI **bsh12361** apyI[dcm+] fnu4HI hinPI bsoFI haeII acil bstul ecoRII SCLFI bstNI mvaI dsav 7601 GGGGGAAACG cac8I

FIG. 48X

7801 TATTACCGCC TITGAGTGAG CTGATACCGC TCGCCGCAGC CGAACGACCG AGCGCAGCGA GTCAGTGAGC GAGGAAGCGG AAGAGCGCC AATACGCAAA ATAATGGCGG AAACTCACTC GACTATGGCG AGCGGCGTCG GCTTGCTGGC TCGCGTCGCT CAGTCACTCG CTCCTTCGCC TTCTCGCGG TTATGCGTTT

mbolI hhal/cfol

sapI hinPI

earI/ksp632I

haeII

acil

mnll

bbvI pleI hinPI hinfI

fnu4HI

fnu4HI

bsoFI bbvI

bsoFI

hhal/cfol

bsiEI

mcrI

bsrBI fnu4HI

bsoFI

acil

aluI

cac8I acil



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maeIII asel/asnl/vspl 7901 CCGCCTCTCC CCGCGCGTTG GCCGATTCAT TAATCCAGCT GGCACGACAG GTTTCCCGAC TGGAAAGCGG GCAGTGAGCG CAACGCAATT AATGTGAGTT GGCGGAGAGG GGCGCGCAAC CGGCTAAGTA ATTAGGTCGA CCGTGCTGTC CAAAGGGCTG ACCTTTCGCC CGTCACTCGC GTTGCGTTAA TTACACTCAA mseI hhal/cfol hinPI cacel acil bsrI cac8I eael tfil asel/asnl/vspl aluI nspBII IInad hinfI mseI tru9I haeIII/palI fnuDII/mvnI cfrI fnuDII/mvnI **bsh1236**I hhal/cfol bsh1236I bstul hinPI bstul thaI acil bslI mnll

FIG. 48Y

8001 ACCTCACTCA TTAGGCACCC CAGGCTTTAC ACTTTATGCT TCCGGCTCGT ATGTTGTGTG GAATTGTGAG CGGATAACAA TTTCACACAG GAAACAGCTA TGGAGTGAGT AATCCGTGGG GTCCGAAATG TGAAATACGA AGGCCGAGCA TACAACACAC CTTAACACTC GCCTATTGTT AAAGTGTGTC CTTTGTCGAT

hpaII

hgicI apyI[dcm+]

banI bsaJI

mnlI

nlaIV bstNI

ecoRII

mvaI

dsav

SCIFI

acil bsrBI

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tru9I
mseI
aseI/asnI/vspI
xmnI
nlaIII asp700
ACTGGTACTA TACGAATTAA (SEQ ID NO.68)
>length: 8120

FIG. 48Z



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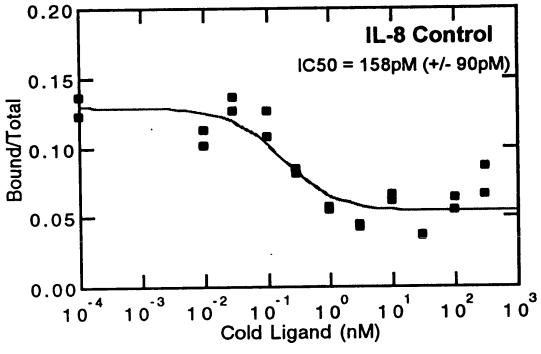


FIG. 49A

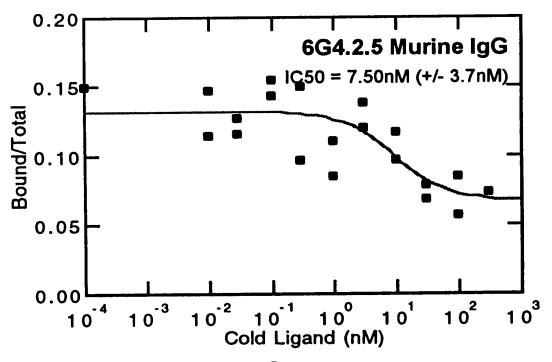


FIG. 49B

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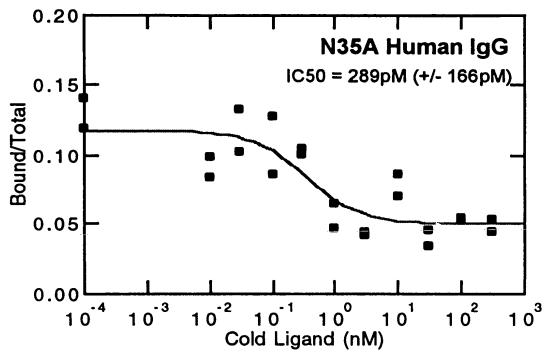


FIG. 49C

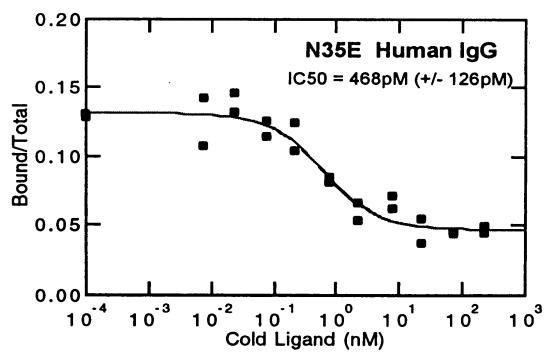
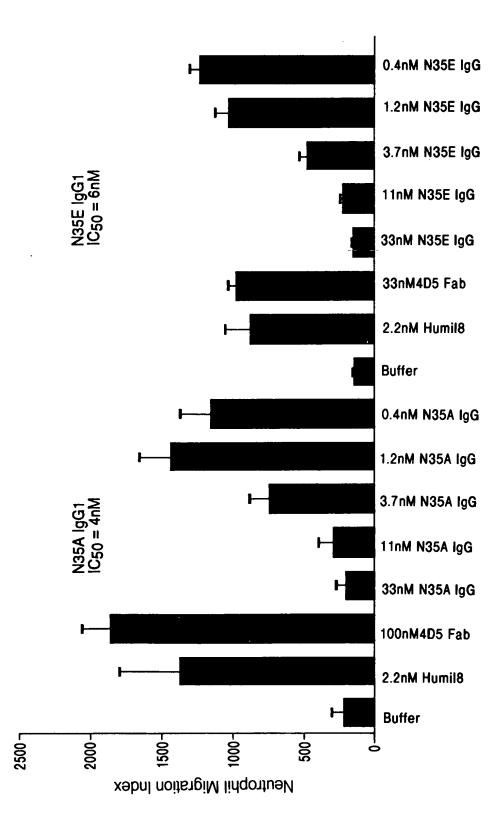


FIG. 49D

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Hsei et a

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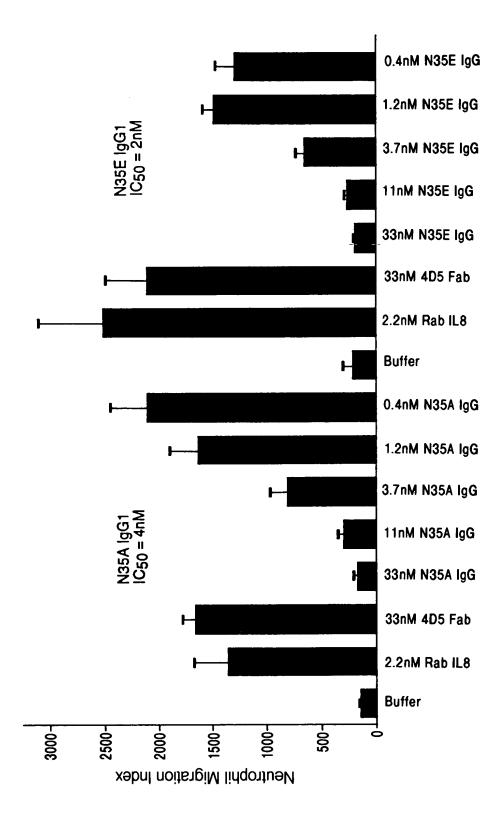
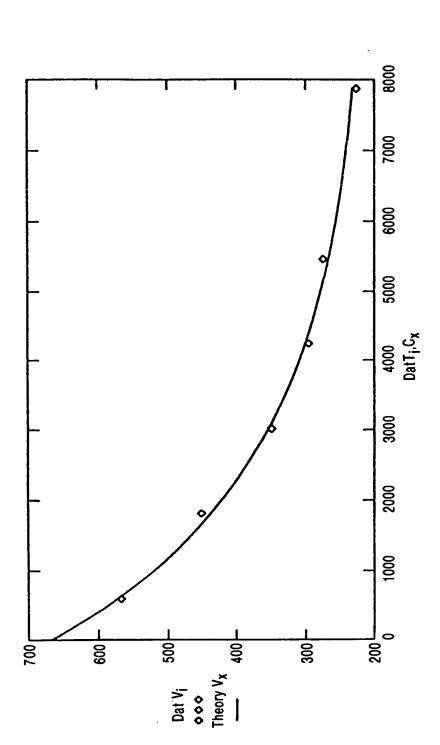


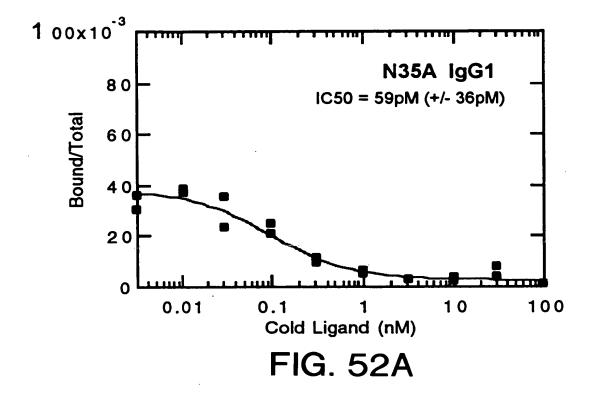
FIG. 50B

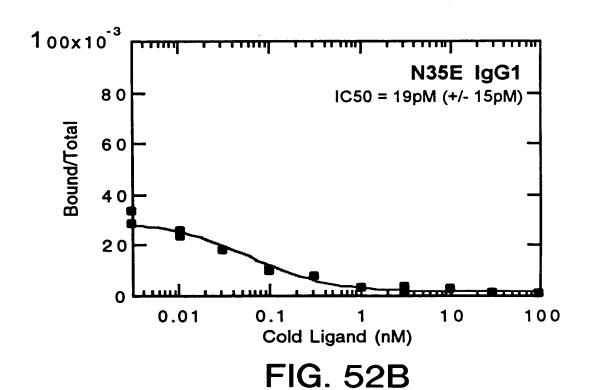






Representative Conc versus Time Plot. Shown is the kinetic data for 6G4V11N35A.IgG1 350pM 88pM 49pM 7.7x10⁻⁵ $1.4x10^{-4}$ 2.9x10-4 kd 3.0×10^{6} $8.7x10^{5}$ 8.3×10⁵ ka Murine 6G4.2.5 IgG2a 6G4V11N35A-IgG1 6G4V11N35E-IgG1 SAMPLE





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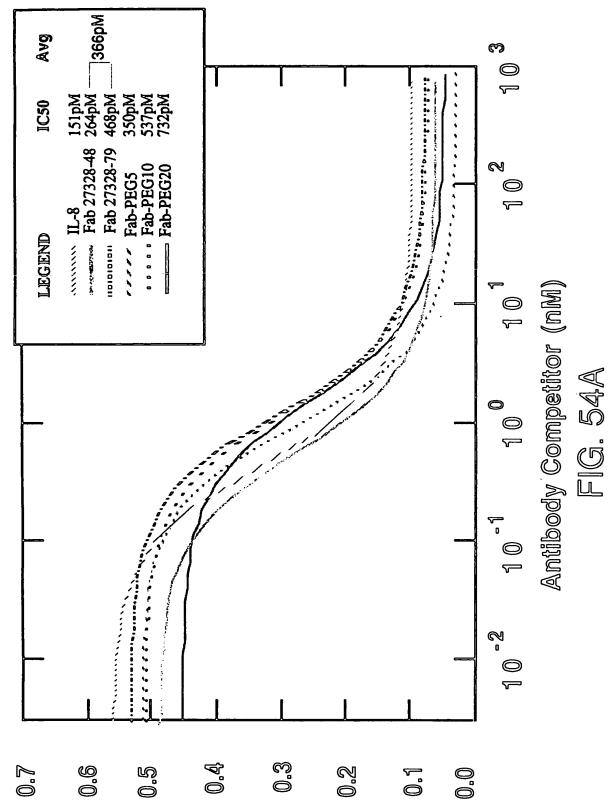
MA																		
781	AAAAGG	ЗСТАТ ССАТА	CTAG GATC	AGGT TCCA	TG AC	AGG'	rga:	TTTT AAAA	ATC	GAA CTT	AAA TTT	GA CT	ATAT TATA	CGC	ATT TAA	TCT AGA	TCT AGA	TGCA ACGT
-1									M	K	K	N	I	A	F	L	L	A
841	TCTATO																	
-11	s M												V					
901	GGCGG!	rggcc	TGGT	GCAG	CC	AGG	GGG	CTCA	CTO	CCG	TTT AAA	GT CA	CCTG	TGC	AGC TCG	TTC'	TGG(CTAC GATG
8																		
961	TCCTTC	CTCGA	GTCA CAGT	CTAT.	AT TA	GCAC	CTG	GGTC	CG!	rca Agt	GGC	CC GG	CGGG	AAT:	GGG CCC	CCT	GGA.	ATGG TACC
28	s F	s s	н_	<u> Y</u>]	Μ	_Н	W	V	R	Q	A	P	G	K	G	L	E	W
1021	GTTGGZ CAACC																	
48	V G																	
1081	TTCACT					GAG	GTT.	PTTG	TG	ľCG	TAT	'GG	ACGT	CTA	CTT	GTC	GGA	CGCA
68	F T	L S	R	D 1	N	s	K	Ņ	T	A	Y	L	Q	M	N	S	L	R
1141	GCTGAC																	
88		D T	A	V	Y	Y	С	A	R	G	D	Y	R	<u>Y</u>	N	G	D	_W
1201	TTCTT																	
108_	FF																	
1261	CCATC																	
128	P S																	
	GGCTG	GGACC	AGTT	CCTG	ΑТ	GAAG	GGG	CTT	GG	CCA	CTG	CC	ACAG	CAC	CTT	GAG	rcco	GCGG
148	G C	r A	K	D .	Y	F	P	E	P	V	T	V	S	W	N	s	G	A
1381	CTGAC																	
	L T			H							-				L		_	_
1441	AGCAGO TCGTCO																	
188	s s	v v	т	V	P	S	S	S	L	G	Т	Q	Т	Y	Ι	С	N	V
1501	AATCA(GGTC	GTTG	TG	GTT	CCA	CTG	TT	CTT	TCA	AC	TCGG	GTT	rag	AAC	ACTO	STTT
	и н			N						K	V	E	P	K	s	С	D	K
1561	ACTCA(Q II) NO.6	59)									
228	т н	TGAGTGTGTA CGGGCGCACT T H T C P P O (SEQ ID NO.70)																

FIG. 53

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ANTIBODY FRAGMENT-POLYMER CONJUGATES AND HUMANIZED ANTI-IL-8 MONOCLONAL ANTIBODIES

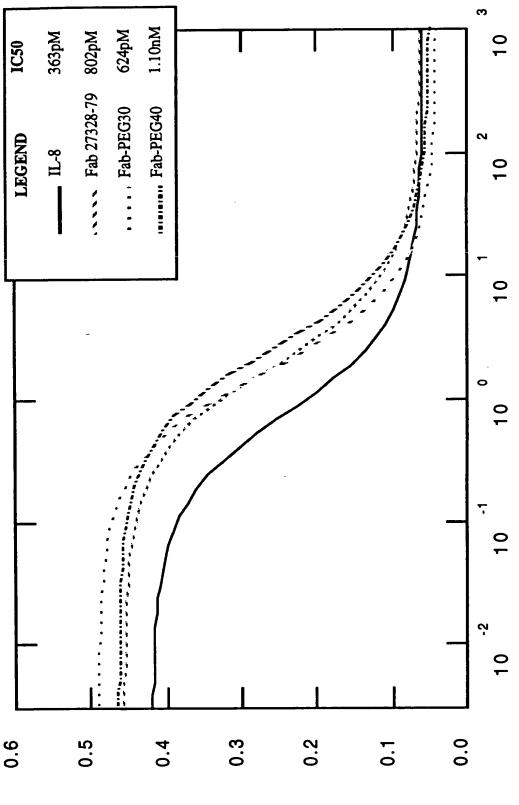
Hsei et al.





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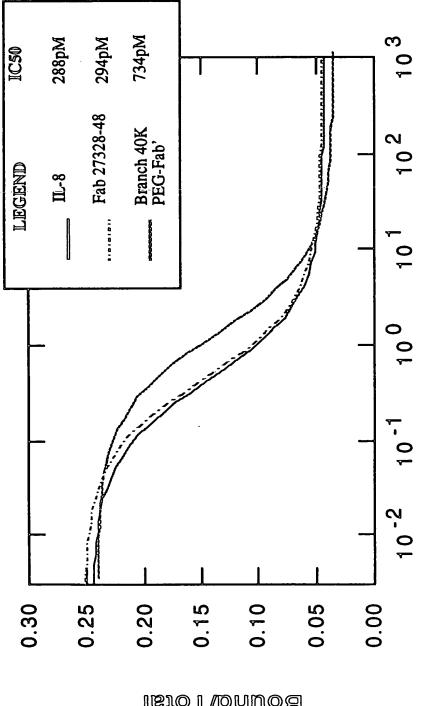


Bound/Total

Antibody Competitor (nM) FIG. 54B



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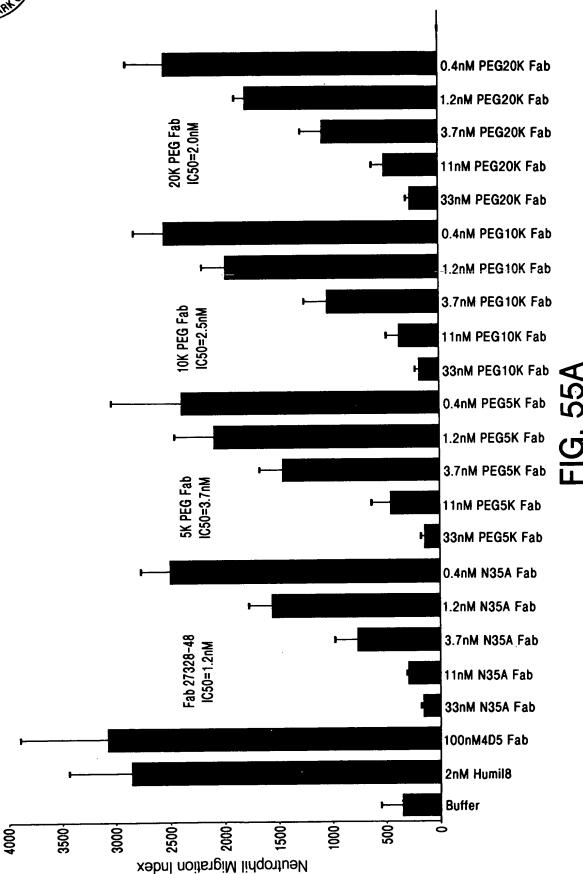


Antibody Competitor (nM)

IstoT\bnuo8



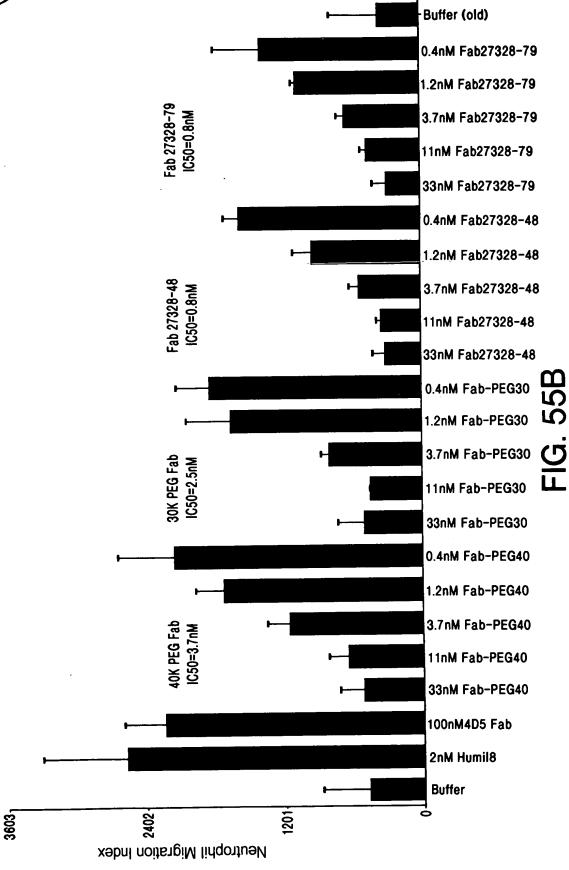
Hsei et al.



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ANTIBODY FRAGMENT-POLYMER CONJUGATES AND HUMANIZED ANTI-IL-8 MONOCLONAL ANTIBODIES

Hsei et al.





Hsei et al.

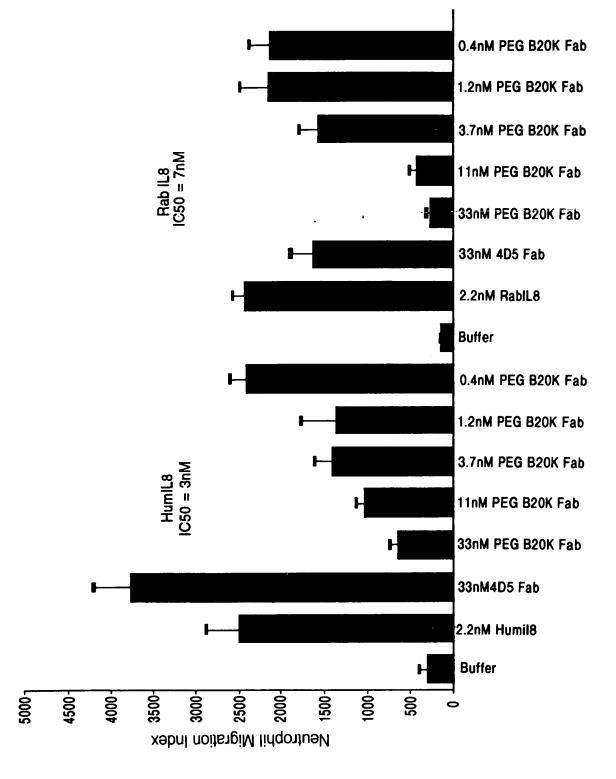
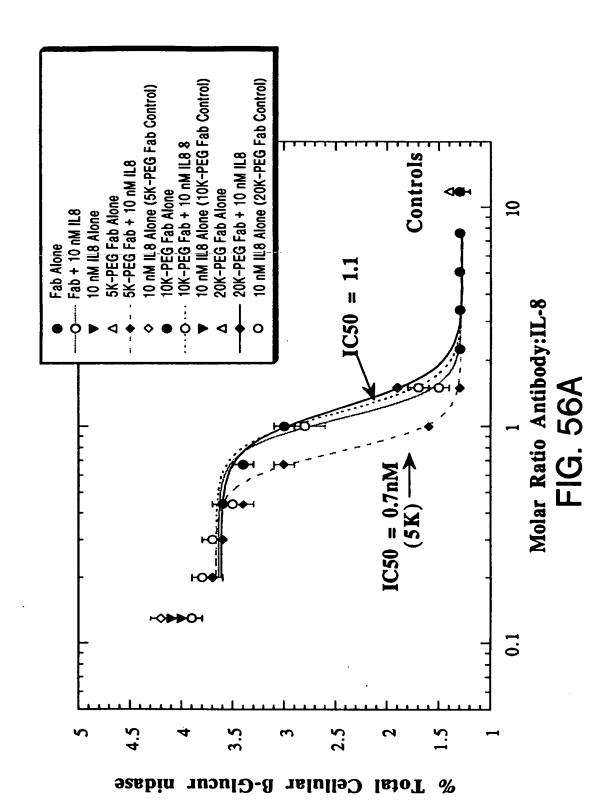


FIG. 55C

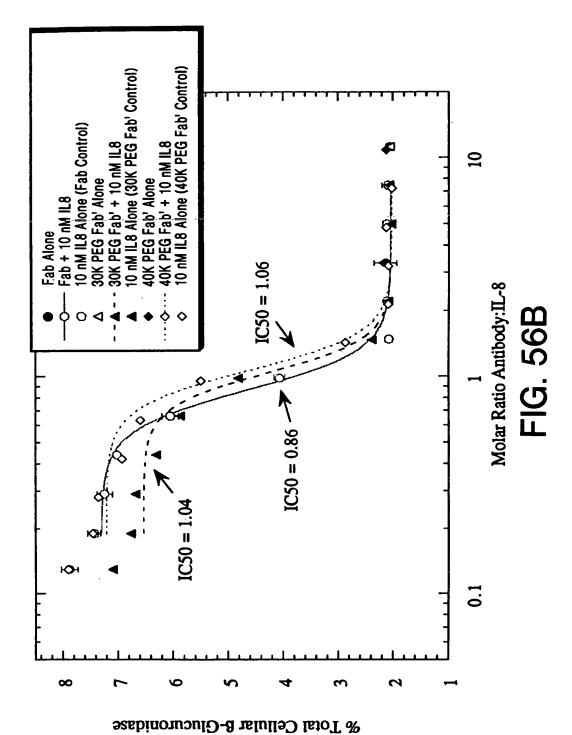


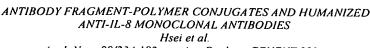
Hsei et al.





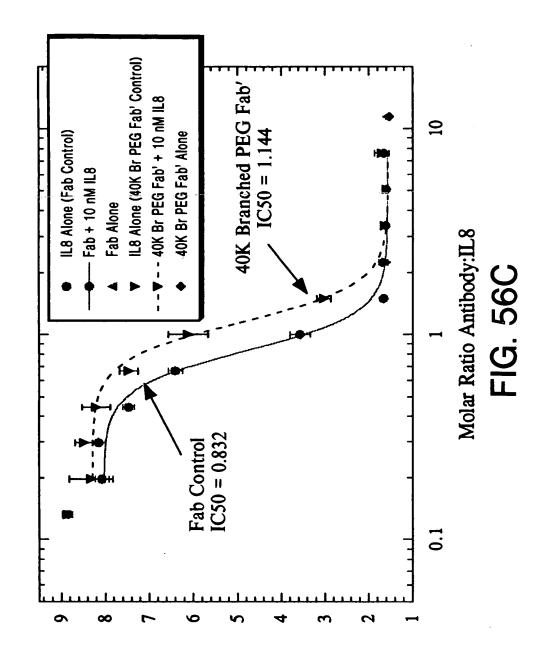
Atty Docket: GENENT.093A Appl. No.: 09/234,182







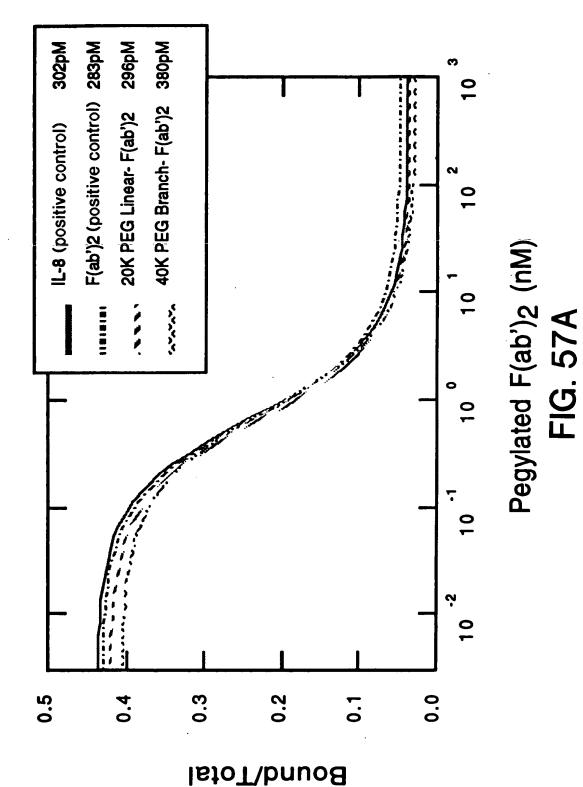


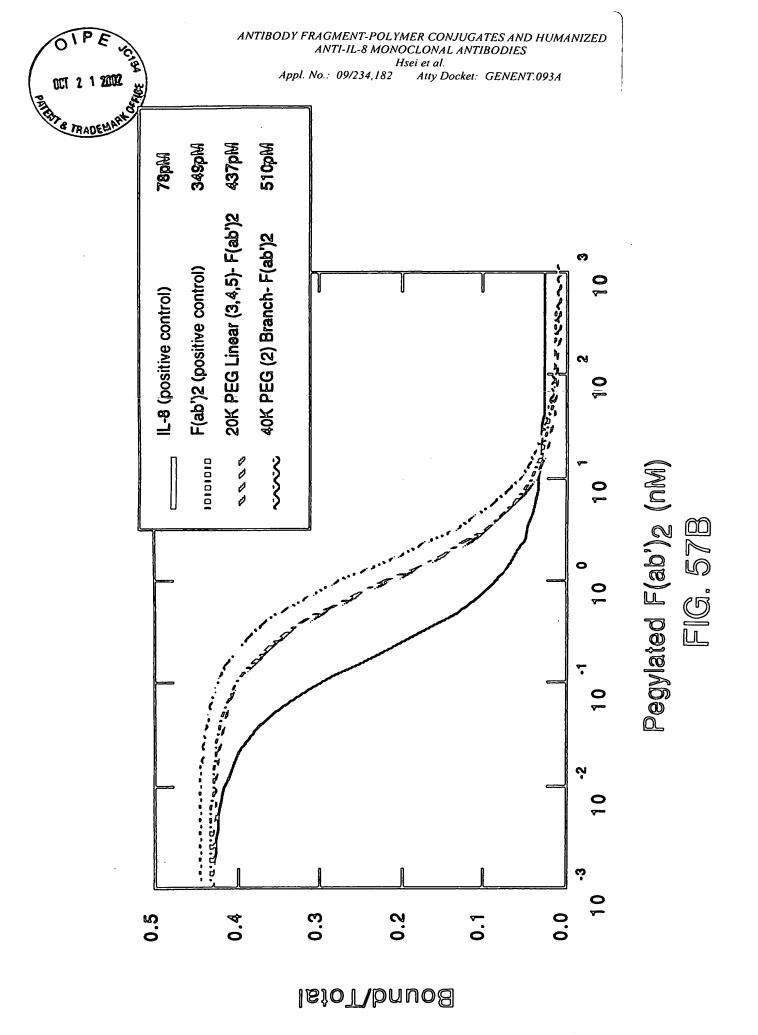


% Total Cellular B-Glucuronidase Activity



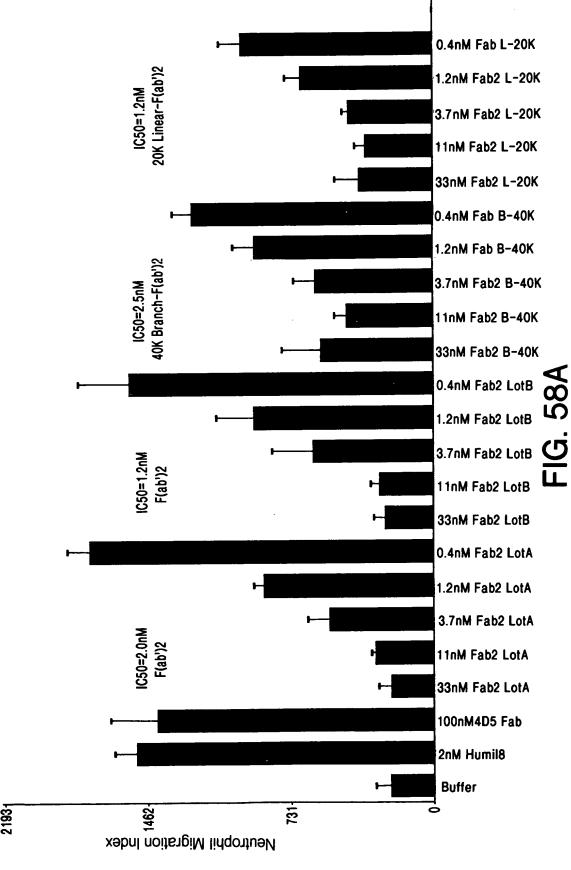
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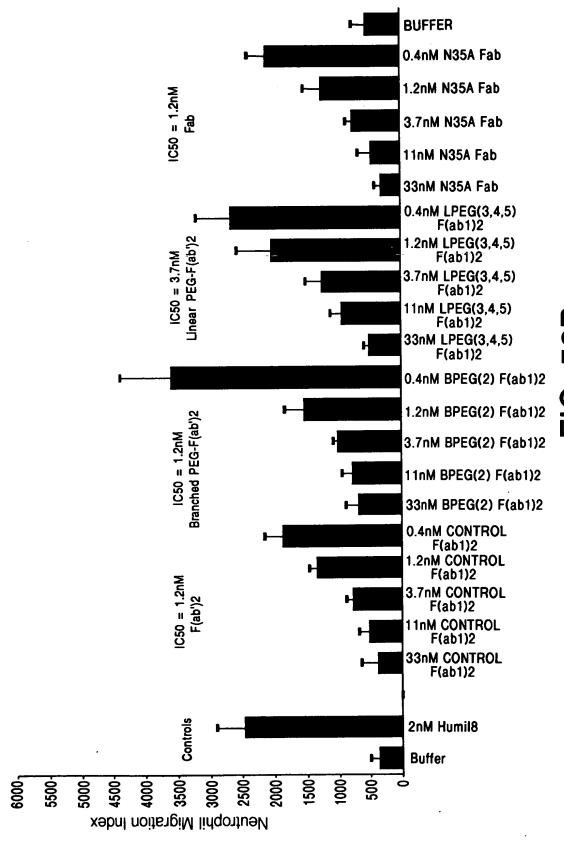


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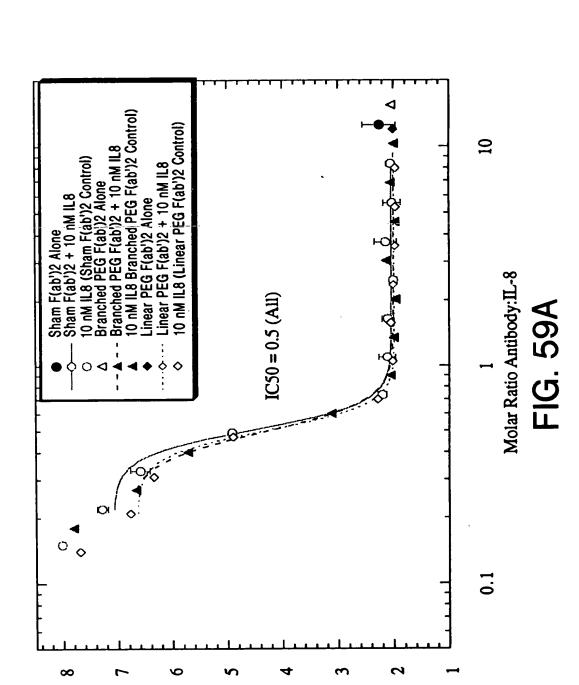


Hsei et al.



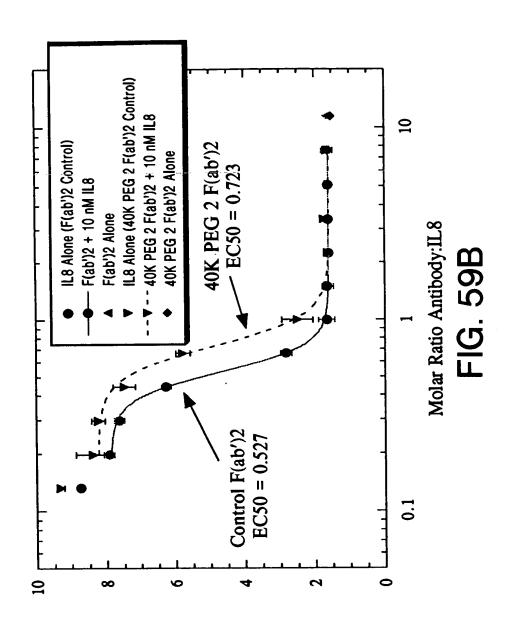


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% Total Cellular b-Glucuronidase



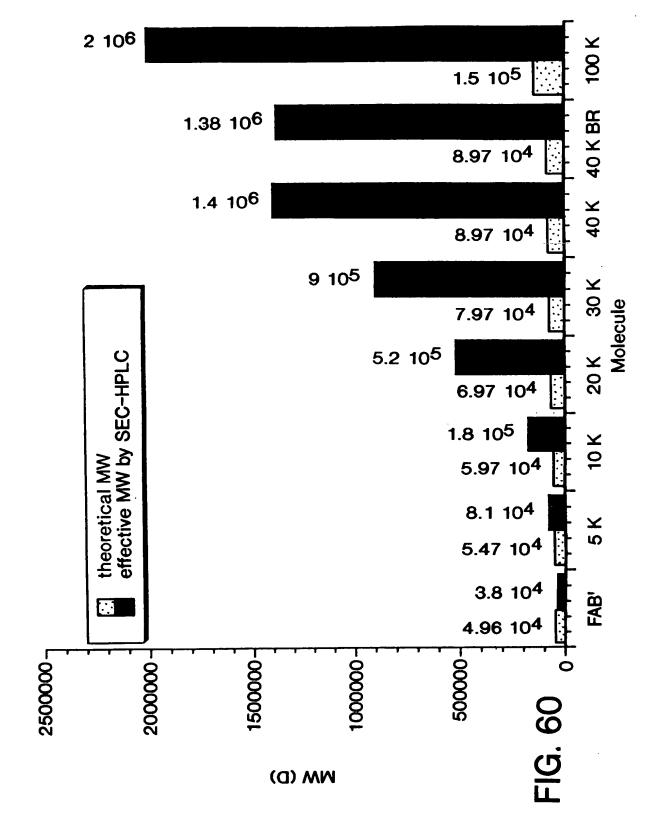


% Total Cellular B-Glucuronidase Activity



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Reduced

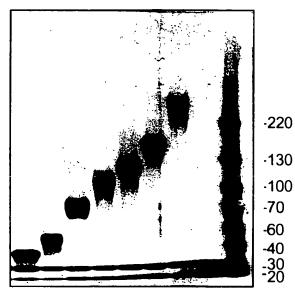
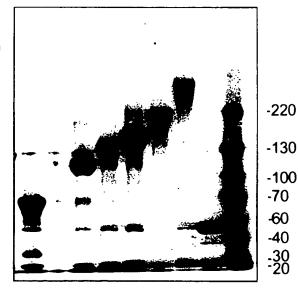


FIG. 61A

-20K -30K -40K -40K branch 100K

Non-Reduced



Fab-PEG-5000

FIG. 61B

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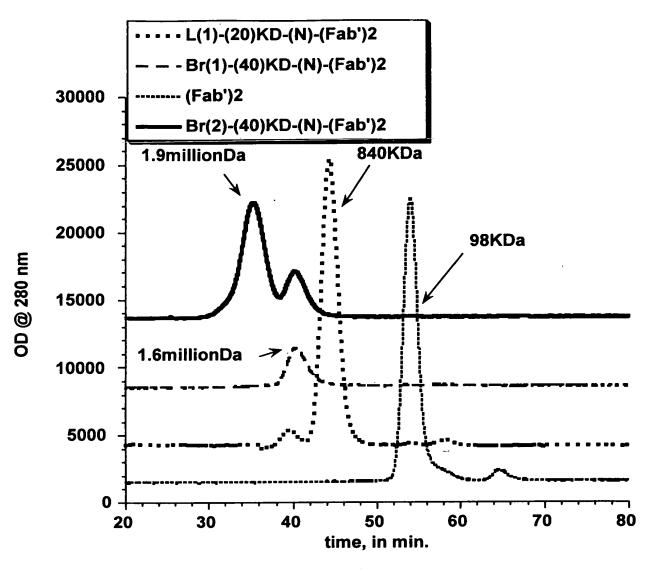
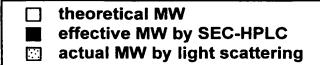


FIG. 62





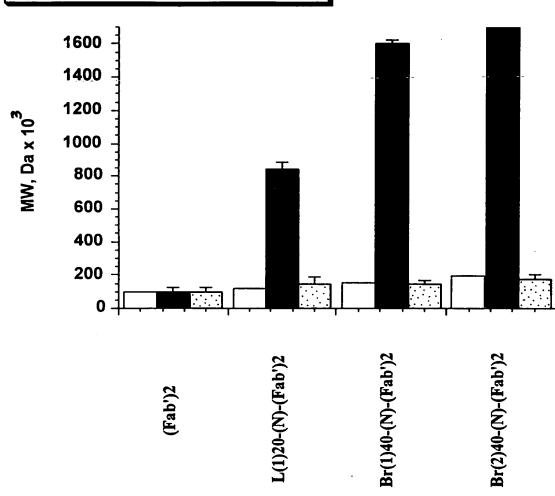


FIG. 63



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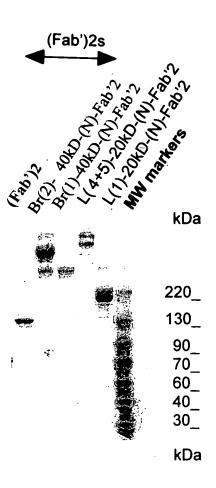
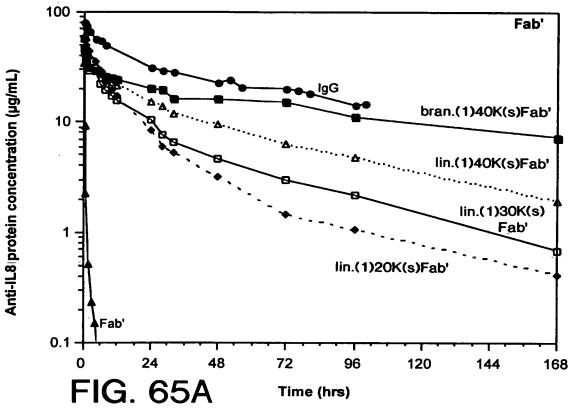
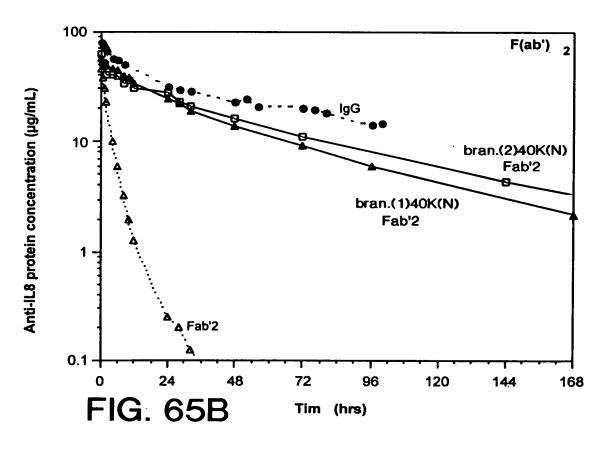


FIG. 64



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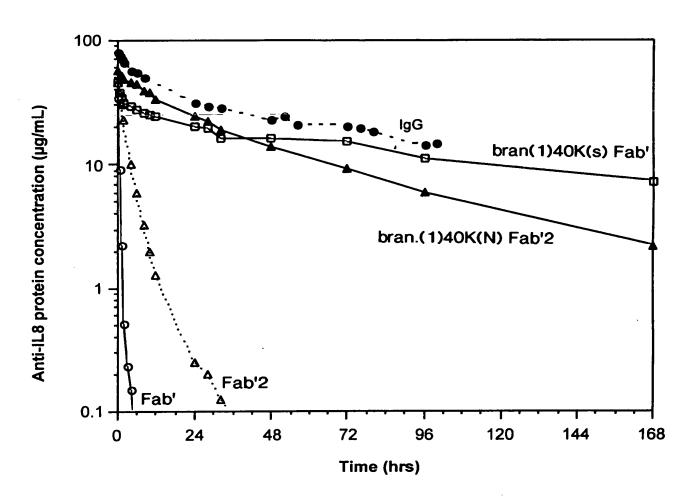
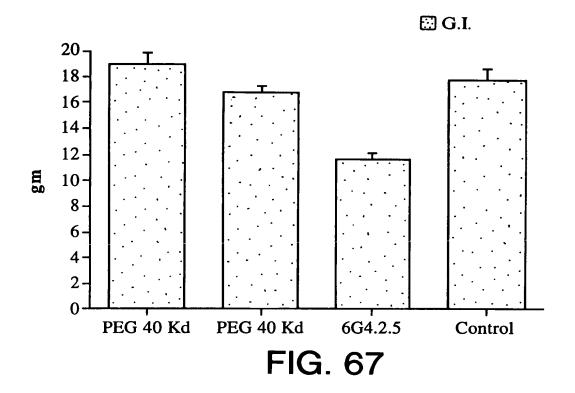
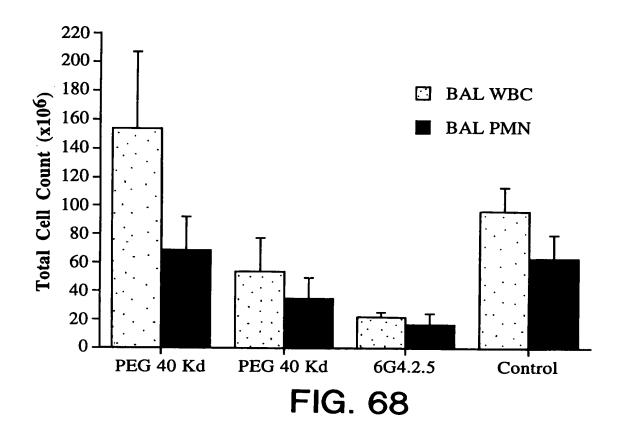


FIG. 66



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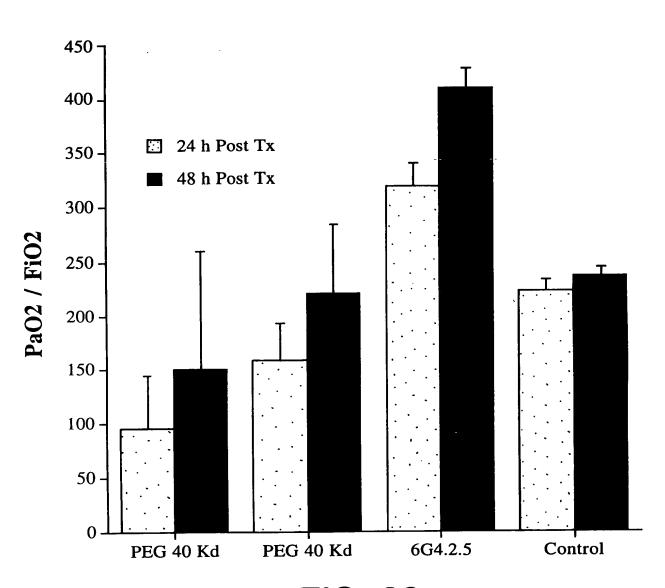


FIG. 69



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Oxygenation in 100% O2 @24 h Post Anti-IL8 Tx

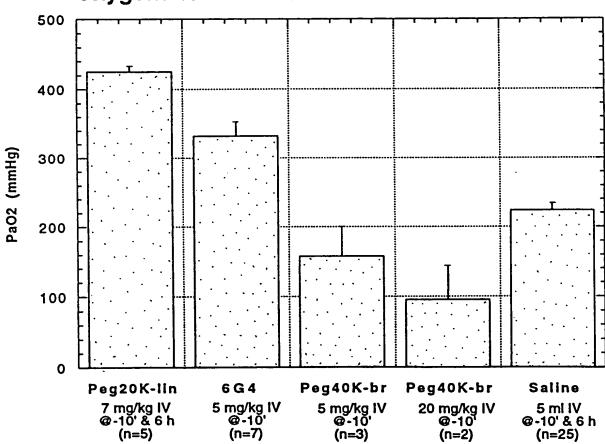


FIG. 70A



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Oxygenation in 100% O2 @48 h post Anti-IL8 Tx 500 400 PaO2 (mmHg) 300 200 100 0 Peg40K-br Peg40K-br Saline 6 G 4 Peg20K-lin 20 mg/kg IV @-10 5 ml IV @-10' & 6 h 7 mg/kg IV @-10' & 6 h (n=5) 5 mg/kg IV @-10' 5 mg/kg IV @-10' (n=16)(n=2)(n=3)(n=7)

FIG. 70B



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Gross Lung Weight to Body Weight Ratio

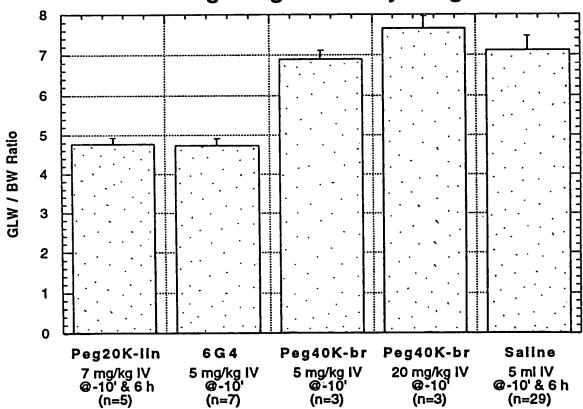


FIG. 70C



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Total WBC in BAL Fluid

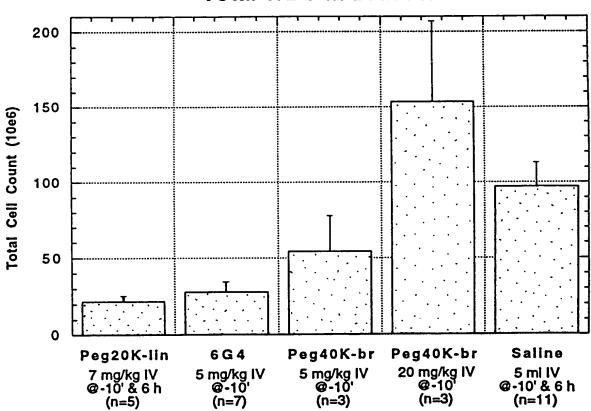


FIG. 70D



Hsei et al.

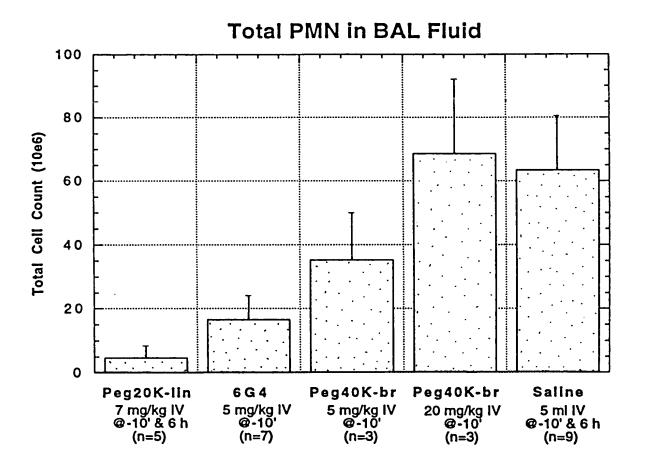
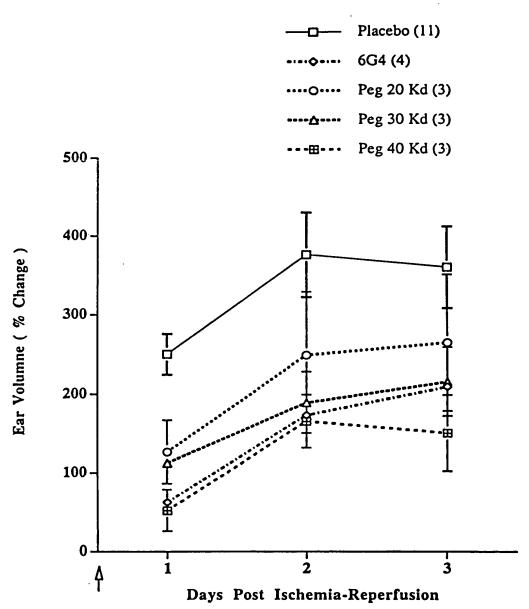


FIG. 70E



Appl. No.: 09/234,182 Atty Docket: GENENT.093A

The Effect of Pegylated Anti-IL-8 in the Rabbit Ear model of Ischemia-Reperfusion Injury



Anti-IL-8 formulations: Single Dose (5 mg/kg) administered IV at time of reperfusion

FIG. 71